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Dr. Vinu M Nampoothiri
Veterinary Surgeon, Veterinary Dispensary, Morayur, Malappuram, Kerala, India

Corresponding Author:
Dr. Vinu M Nampoothiri
Veterinary Surgeon, Veterinary Dispensary, Morayur, Malappuram, Kerala, India

Ghrelin and its role in animals

Dr. Vinu M Nampoothiri

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Abstract
Ghrelin is a 28-amino acid peptide hormone secreated mainly from stomach in animals. Ghrelin stimulate release of growth hormone. Ghrelin works with the help of ghrelin receptors. Ghrelins main function is to increase hunger and regulate feed intake. Ghrelin performs other functions like stimulation of gastric acid secreation, helps in the regulation of carbohydrate metabolism, increase body fat content, corticosteroid release, reproductive functions and metabolic adaptation of lactation also. All these functions of ghrelin are discussed in detail in this article.

Keywords: Ghrelin, hormone, receptor, feed

Introduction
The word ghrelin can be actually split up into two i.e. “Ghre” which means grow and “Relin” which means hormone. Ghrelin is a 28-amino acid peptide modified at its third residue, a serine (Ser3), by a middle-chain fatty acid, n- octanoic acid (Ueno *et al*., 2005) [29]. Ghrelin was discovered by Kojima in 1999 [10]. Ghrelin has been found in fishes, amphibians, birds, and many mammals. Ghrelin is secreated from fundic part of the stomach. Ghrelin is primarily expressed in the X/A- like cells of the oxyntic gland in the stomach of monogastrics and the abomasum of ruminant animals (Date *et al*., 2000) [3]. There are lower levels expressed in the small intestine, the pancreas, lymphocytes, placenta, kidney, lung, brain, pituitary and gonads (Barreiro and Tena-Sempere, 2004) [2]. Growth hormone release from the anterior pituatary is under the control of two hormones growth hormone releasing hormone and somatostatin from hypothalamus. But later found that some opiod peptide derivatives had weak growth hormone releasing activity. It was found that small synthetic peptidyl and non-peptidyl molecules called growth-hormone secretagogues (GHSs) have growth hormone releasing action (Smith *et al*., 1997). Release of growth hormone by GHS is through GHS receptors (GHS-R). The GHS-R exists in two isoforms, 1a and 1b, the former of which is the functional receptor for ghrelin (Kojima *et al*., 1999) [10]. GHSs and ghrelin stimulate GH release by increasing intracellular Ca^{2+} levels through the activation of the phospholipase-IP3 pathway.

Ghrelin increase hunger through its action on hypothalamic feeding centers. Ghrelin occurs in 2 forms
a) n- octanylated/ acylated (AG)
b) des acylated (DAG)
The main function of AG is GH secreation and function of DAG is lipogenesis.

Ghrelin Receptors
Ghrelin receptors are of two types, one is centrally placed one and the other one is peripherally placed one. Receptors were located in hypothalamus, pituitary, hippocampus, liver as well as vagal afferent endings throughout the GI tract. Ghrelin is the only identified endogenous ligand for GHS-R (Growth Hormone Secretogogue Receptor). GHS-R is concentrated in the pituitary cells where ghrelin promotes GH releasing activities (Lorenzi *et al*., 2009) [14]. GHS-R had two subtypes – GHS-R1a & GHS-R1b (Barreiro and Tena-Sempere, 2004) [2]. GHS-R1a expressed in negative energy balance (Litwack *et al*., 2008) [13]. Ghrelin acts on the lateral nucleus (Hunger/feeding center) and stimulate appetite. Ghrelin acts on the arcuate nucleus to regulate appetite.

Ghrelin and regulation of feed intake

Ghrelin is a strong orexigenic and adipogenic molecule (Nakazato *et al*., 2001) [18]. Hypothalamus and GI tract are closely linked in the regulation of feed intake. Fos protein is a protein seen in areas where the ghrelin receptor is distributed. It was found that expressing antisense ghrelin receptor mRNA decreases GH secreation, food intake and body fat mass in transgenic rats (Shuto *et al.,* 2002) [23]. Ghrelins orexigenic activity is independent of GH signaling pathway (Nakazato *et al.,* 2001) [18]. Continuous intra cerebro ventricular (ICV) administration of ghrelin induces food intake and an increase in fat mass, leading to weight gain (Tschop, 2000) [28]. Neuropeptide Y (NPY) and agouti related protein (AgRP) are the ghrelin responsive orixigenic peptides in the hypothalamic arcuate nucleus (ARC). ICV administration of ghrelin shown to induce Fos expression in 39% of NPY/AgRP-expressing neurons and increase both NPY and AgRP mRNA levels in ARC (Seoane *et al*., 2003) [22].

Circulating ghrelin levels are increased by fasting and decreased by feeding in rats (Toshinai *et al*., 2001) [27]. In addition, hyperglycemia reduces circulating ghrelin levels (Nakagawa *et al*., 2002) [17]. These reports suggest that ghrelin has a role in the regulation of appetite. In sheep on programmed feeding regimens, the pre-prandial increase in plasma ghrelin levels (and the rise with pseudo-feeding) is followed by a rise in plasma GH levels (Sugino *et al*., 2002) [25], strongly suggesting that the former stimulates the latter. Wertz *et al*., (2004) [30] compared the plasma ghrelin level of fast and fed steer and he noticed that the plasma level of ghrelin on fed steer was lower than that of fast steer. Miura *et al*., (2014) [15] studied the effect of feeding on ghrelin level in cows and found higher level of ghrelin in plasma during fasting time and 4hrs after feeding compared to one hr after feeding.

Salfen *et al*., (2004) [21] found that exogenous ghrelin has a variety of endocrine effects and shows potential in increasing body weight gain in pigs during weaning. If ghrelin can decrease the length of weaning anorexia and increase body weight gain during the weaning period, pigs will potentially be able to better resist pathological and environmental challenges during this time. But in contrary Wu *et al*., (2008) [32] found that exogenous ghrelin at the dosage of 1 μg/d pig could cause a variety of behavioral effects, but not improve performance of weanling piglets.

Ghrelin and other gastrointestinal effects

Intravenous administration of ghrelin to rats stimulates gastric acid secretion and gastric motility (Kamegai *et al.,* 2001) [8]. Ghrelin affects gastric function through vagus nerve (Ueno *et al.,* 2005) [29]. Ghrelin protect against ethanol induced gastric ulcers in rat (via nitric oxide dependent central mechanism) (Sibilia *et al.,* 2003) [24]. Chicken ghrelin caused contractile responses in smooth muscle strips isolated from various parts of the GI tract (Kitazawa *et al.,* 2007) [9]. Ghrelin causes gastric contraction in japanese quail (Kitazawa *et al.,* 2009) [9]. But in rabbits ghrelin does not induce contraction (Peeters *et al*., 2005) [19].

Ghrelin and carbohydrate metabolism

Ghrelin increases circulating glucose levels via GH release, increasing insulin resistance and stimulating gluconeogenesis (Muller *et al.,* 2001) [16]. Ghrelin stimulate Insulin Receptor Substrate 1 (IRS1) as well as its downstream signaling molecules. It inhibits Akt activation and opposed effect of insulin on rate-limiting enzyme of gluconeogenesis, phosphoenolpyruvate carboxykinase, therefore upregulating gluconeogenesis (Korbonits *et al*., 2004) [11]. Krueger and Melendez (2012) [12] observed lower concentrations of serum insulin on ghrelin (5 microgram/kg body weight intramuscularly) treated group compared to the untreated group.

Ghrelin and adipose tissue

The chronic ghrelin administration has been shown to increase body fat content in rodents (Tschop, 2000) [28]. Ghrelin treated animals do not increase their weight but increase their fat tissue content as assessed by MRI (Wren *et al*., 2004) [31]. Ghrelin increases levels of PPAR gamma mRNA, which stimulates differentiation of preadipocytes *in vitro*. According to Thompson *et al., (*2004) [26] ghrelin infused to bone marrow improved bone marrow fat cell proliferation.

Ghrelin and corticosterone releasing activity

Ghrelin stimulates the corticosteroid release in humans, pigs, cows, mice and rats. Ghrelin receptors are present in adrenal gland (Rucinski *et al.,* 2009) [20]. Azzam *et al*., (2017) [1] found that hypothalamic pituitary adrenal (HPA) axis mediated elevations in ghrelin plasma concentration require increased peripheral cortisol levels, independent of central elevation of adreno cortico tropic hormone (ACTH) and possibly corticotropin releasing hormone (CRH) levels and concluded that further studies are needed to elucidate whether a neuroendocrine feedback system between the HPA axis and ghrelin secretion exists.

Table 1: Comparison of ghrelin effect across vertebrates

Effect	Mammals	Aves	Amphibians	Fishes
GH release	Stimulate	Stimulate	Stimulate	Stimulate
Corticosteroids release	Stimulate	Stimulate	Stimulate	Stimulate
Feeding	Stimulate	Inhibit	-	Stimulate
Plasma level during fasting	Increase	Increase	Increase	Increase
GI contraction	contraction	contraction	-	No effect
Drinking	Inhibit	Inhibit	No effect	Inhibit

(Modified from Kaiya *et al*., 2013) [7].

Ghrelin and Reproduction

Ghrelin expression is high during diestrus time (Barreiro and Tena-Sempere, 2004) [2]. Diestrus is the period of corpus luteum formation. Ghrelin expression was located in the ruptured follicle, the corpus luteum (CL) (Barrerio and Tena-Sempere, 2004).CL produces progesterone. So from this it can be assumed that ghrelin and progesterone had a parallel production pattern with regard to reproductive system. Ghrelin expression is higher during the beginning of gestation and also acts to maintain the pregnancy (Garcia *et al*., 2007) [5].

Ghrelin in metabolic adaptation of lactation

Ghrelin is also involved in the control of prolactin secretion, which stimulates milk production (Barreiro and Tena-Sempere, 2004) [2]. Ghrelin causes an increase in food intake, increase digestion and absorption. This results in an increased propionate and amino acid absorption from gut. Ghrelin helps in the mobilization of tissue reserves during lactation. Ghrelin also increases lipoprotein lipase activity in the mammary gland (Felix, 2010) [4]. when ghrelin levels were increased, milk production also increased which then caused the weight of the offspring to also increase (Gottero *et al*., 2004) [6]. Felix (2010) [4] found that high producing cows (12,923 ± 217 kg of milk) had lower levels of plasma ghrelin (45.1 ± 8.9 pg/ml)

compared to the low producing cows (10,332 ± 322 kg of milk; 73.3 ± 8.5 pg/ml of ghrelin), but the high producers produced more milk in comparison to the low producers and he concluded that although the results were the opposite of what we anticipated, they may be the result of prioritized nutrient partitioning in an attempt to maintain a favorable energy status.

Conclusion

Ghrelin is a recently discovered endogenous peptide that participate in energy homeostasis by stimulating GH secretion. Ghrelin controls feeding behavior. Ghrelin is an ultimate anabolic hormone. Along with its above mentioned effects ghrelin found to have effects on the cardiovascular system, sympathetic system etc. But only little information is available about its physiology and function.

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