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Minireview

The Physiological potentials of Ghrelin in enhancing Feed intake in Livestock

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ABSTRACT

Ghrelin is an orexigenic protein with a unique lipid chain modification and is known to be an important gut-brain signal for appetite control and energy balance. It is neuroendocrine hormone secreted mainly by the oxyntic cells of gastric fundus and travels to the brain. There it interacts with both the hypothalamus (the brain's physiological eating center) and the brain's pleasure centers to arouse hunger. The ghrelin receptor, growth-hormone secretagogue receptor type 1a, is able to bind acylated ghrelin. The first recognised effect of ghrelin was the induction of growth hormone release from the somatotroph cells of the anterior pituitary. It is also expressed in the pancreatic islets, hypothalamus, pituitary and several tissues in the periphery. The aim of this review is to see some of the effects of ghrelin on feeding behaviour in selected livestock species.

INTRODUCTION

Ghrelin is a 28-amino acid peptide in monogastric species, a 27-amino acid peptide in ruminants (Dickin et al.2004) except in the bovine where it is a 29-amino acid peptide (Niemann et al., 2011). It is primarily produced by oxyntic cells in the stomach or abomasum with smaller amounts produced by the intestine and pancreas (Hayashida et al. 2001, Hosoda et al. 2006). Ghrelin, a ligand for the growth hormone secretagogue receptor (GHSR) (Kojima et al., 1999, Ziru et al., 2012), was discovered in 1999 after a research done on rat stomach produced an extract that activated the receptor (Kojima et al., 1999). The stomach has been recognized as the greatest source of ghrelin produced chiefly by endocrine cells known as P/D1 cells Ariyasu et al., 2001). Ghrelin stimulates the secretion of GH increases food intake and in turn produces gain in weight (Takaya et al., 2000). Apart from its effect on GH, it has various important biological actions like regulation of cardiovascular functions (Shimizu et al., 2003, Nagaya et al., 2004), stimulating gastric acid synthesis and secretion (Masuda et al., 2000), modulating cell proliferation and survival (Baldanzi et al., 2002, Kageyama et al., 2005) energy balance and metabolism. It is also associated with regulation of blood glucose, obesity and sleep wake cycle.

Both animal experiments and clinical studies demonstrate that ghrelin induces a rapid increase in food intake in rodents and humans (Muccioli et al., 2002).

In mammals, the distribution of the ghrelin receptor is most extensively studied in laboratory mammals.

Although a widespread distribution of the ghrelin receptor has been demonstrated, the highest levels of expression (ghrelin receptor mRNA) has been detected in the pituitary gland (Gnanapavan et al 2002, Ueberberg et al 2009), which is consistent with the role of ghrelin in the regulation of GH release. In general, the ghrelin receptor transcripts have also been detected in brain areas linked to energy homeostasis such as the hypothalamus, hippocampus, substantia nigra, ventral tegmental area, and dorsal and median raphe nuclei

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(Bennett et al 1997, Guan et al 1997 Kageyama et al 2005, Zigman et al 2006, Chen et al 2009), although clear species differences in the distribution, e.g., between lemurs and rats, have been reported (Mitchell et al. 2001)

Ghrelin is the only known peripherally produced and centrally active orexigenic hormone that is considered to be an important gut-brain signal for appetite control and energy balance (Solomis and Korbonits, 2014). The most striking physiological effects of ghrelin, independent of GH releasing activity, is the stimulation of appetite and feeding behavior. Infusion of ghrelin, either intracerebroventricularly or peripherally, into mice or rats stimulates feeding behavior and if the injections are given long enough the animals will gain weight (Tschop et al. 2000, Wren et al. 2000, Kamegai et al. 2001). Antagonism of ghrelin receptors will reduce ghrelin's effects on food intake and body weight gain (Asakawa et al. 2003).

History and characteristics of Ghrelin

Ghrelin was identified in 1999 in a study which was designed to search for an endogenous ligand for an orphan receptor, the type 1a growth hormone secretagogue receptor (GHS-R1a). Ghrelin acts on the ghrelin receptor (GHS-R) and activates phospholipase C to generate IP3 and diacylglycerol, resulting in an increase of intracellular Ca^2, indicating that the ghrelin receptor is coupled to a Gq subunit (Bacha and Arslanian, 2005).

The signal transduction pathway following ghrelin receptor activation was investigated using HepG2, a hepatoma cell line that responds to ghrelin. Ghrelin upregulates several activities that are also potentiated by insulin, including tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1), association of the adaptormolecule growth factor receptor-bound protein 2 with IRS-1 and stimulates mitogen-activated protein kinase activity.Ghrelin, which was derived from rat stomach extracts, was found to be able to activate this receptor and to stimulate growth hormone release from the pituitary in a dose dependent manner. The name ghrelin comes from this physiological effect: Ghre is the Proto-Indo-European root of the word "grows" (Kojima et al.1999). Subsequently ghrelin was demonstrated to have other biological activities, such as increasing appetite and food intake, and it has been given the nickname, the "hunger hormone (Broglio et al., 2003).

Several researches have shown that ghrelin is involved in the regulation of energy homeostasis. Ghrelin levels increase before and decrease after meals, principally playing a role in meal initiation and satiety in an inverse pattern to that of insulin (Tschop et al. 2000; Cummings et al.2001; Wren et al.2001; Bacha and Arslanian, 2005). In addition, ghrelin is involved in the regulation of energy balance by increasing food intake and reducing fat utilization (Tschop et al. 2000; Nakazato et al.2001; Wren et al. 2001).

Moreover, ghrelin controls glucose metabolism (Patel et al. 2006) and possibly is involved in the regulation of insulin activities in man (Murata et al. 2002). However, unlike insulin, ghrelin inhibits protein kinase B and partially reverses the downregulating effect of insulin on phosphoenolpyruvate carboxykinase (PEPCK) mRNA expression, a rate-limiting enzyme of gluconeogenesis (Gil-Compos et al., 2006).

Likewise, ghrelin appears to be related with the regulation of energy expenditure (St-Pierre et al. 2004; Zigman et al. 2005; Maffeis et al. 2006). Signalling by circulating ghrelin is mediated downstream by neurons of the arcuate nucleus (ARC) of the hypothalamus; in particular, neurons expressing neuropeptide Y (NPY) and agouti-related protein (AgRP), two potent orexigenic peptides (Guan et al. 1997; Kamegai et al. 2001; Chen et al. 2004; Gropp et al. 2005). One of the principal way by which ghrelin can influence dietary intake is based on the feature that it acts as a hormone, secreted primarily by the stomach and small intestine into the bloodstream, from which it gains access to neuropeptide Y /AgRP neurons in the medial ARC across an incomplete blood brain barrier at that site. Additional effects may result from circulating ghrelin accessing its receptor at circumventricular sites in the hindbrain, which may subsequently affect ARC neuronal activity via ascending projections (Gil-Compos et al., 2006).

Unlike ghrelin, most other hypothalamic peptides—for example, neuropeptide Y (NPY), agouti-related peptide (AGRP), orexins, melanin-concentrating hormone (MCH), and galanin— that stimulate feeding when administered centrally are ineffective when administered into the periphery. Ghrelin is the first identified circulating hormone that promotes feeding following systemic administration (Hosoda et al., 2002)

Effects of Ghrelin on Feed Intake in Livestock

Ghrelin is known to transport hunger signals from periphery to the central nervous system via the vagus nerve. Research has shown that intravenous and subcutaneous injections of ghrelin in rodents resulted in increase in their food intake and thus increase in their body weight gain and decrease in fat utilization (Jain, 2014)

The first recognised effect of ghrelin was the induction of growth hormone (GH) release from the somatotroph cells of the anterior pituitary (Takaya et al., 2000). Also, by acting centrally or via vagal afferents, ghrelin can activate hypothalamic arcuate neurons that secrete the orexigenic peptides neuropeptide Y (NPY) and agouti-related peptide, and inhibit the anorexigenic neurons secreting α-

melanocyte-stimulating hormone (α-MSH) (Horvath et al., 2003).

Arcuate neurons project to paraventricular, lateral hypothalamic and other nuclei, as well as orexin in the lateral hypothalamus, which could contribute to the orexigenic effects of ghrelin.

Ghrelin is the first known peripheral hormone that can induce orexigenic effects through acting on hypothalamic pathways; moreover, it is active even with peripheral administration, in contrast to most orexigenic peptides which are only active when injected into the brain (Kojima et al., 1999). Ghrelin is considered to be the peripheral counterpart of insulin and leptin, as it exerts opposite effects compared to these hormones. A study on healthy volunteers demonstrated that ghrelin reduces glucose-stimulated insulin secretion.

Inadequate nutrient intake relative to demand for maintenance and production can result in economic loss from poor production efficiency and metabolic disorders. Therefore, understanding feed intake regulation and energy expenditure in livestock is important.

In rodents, ghrelin stimulates feed intake through neuropeptides in the hypothalamus (Nakazato et al., 2001) and is reported to influence energy metabolism and body composition (Tschöp et al., 2000). Most research that has been conducted with livestock to evaluate the relationship of plasma ghrelin with feed intake restriction has been done with short-term periods of complete feed deprivation without sufficient length to result in differences in body composition. Wertz-Lutz et al. (2006) observed elevated plasma ghrelin concentrations that persisted for 48 h in mature beef cattle completely deprived of feed. Length and severity of the nutrient restriction may influence plasma ghrelin concentrations. More often than complete feed deprivation, ruminant livestock encounter periods of prolonged, moderate nutrient restriction, whereby nutrient resources are limiting relative to expected production (Arnold et al., 2006)

Ahmed and Harvey 2002 and Baudet and Harvey 2003, however reported that ghrelin's effects upon feeding behavior are not as clearly defined in avian species as they are in rodents and humans and other domestic species. Following the discovery of ghrelin in birds, there has been a report of peripherally injected ghrelin stimulating feeding behavior in birds and that was reported in adult quail (Shousha et al. 2005). Furuse et al. 2001, Saito et al. 2002 and Saito et al. 2005 reported that intracerebroventricular injection of ghrelin into broiler chicks or peripheral injection of ghrelin into chicks reduced feed intake while Kaiya et al. 2007 reported no difference in feed intake following intracerebroventricular injection of ghrelin. Sharyar and Lofti, (2016), however, reported decrease in feed intake following administration of ghrelin receptor antagonist in broiler chicken.

Ghrelin-positive cells are present in the abomasum and ruminal tissue of cattle (Hayashida et al., 200, Gentry et al., 2003), and ghrelin administration increases the time spent eating and also increases dry matter intake in them (Borner et al., 2013).

Hemmann et al., 2011 reported a peak in total ghrelin before feeding in horses. Gordon and McKeever, 2005 also reported a peak in ghrelin concentration in horses after concentrate feeding during free-choice access to hay. Hemmann et al. 2011, however, did not notice any clear decline after overnight fasting. They reported that some short-term peaks may have been hindered by the 2 hours sampling intervals they adopted because ghrelin is released rather abruptly (e.g. only 20–30 min in humans) before a meal (Cummings et al., 2001, Deplort, 2013).

CONCLUSION

In conclusion, evidence suggests that ghrelin plays an important role in the regulation of appetite and food intake and most probably in energy expenditure. The mechanism of action for ghrelin involves several pathways including hormonal actions on hypothalamus and hindbrain neurons. It is therefore concluded that administration of ghrelin to livestock may enhance feed-intake, improve weight gain and enhance food security particularly in developing countries.

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