Secretory pattern and regulatory mechanism of growth hormone in cattle

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ABSTRACT

The ultradian rhythm of growth hormone (GH) secretion has been known in several animal species for years and has recently been observed in cattle. Although the physiological significance of the rhythm is not yet fully understood, it appears essential for normal growth. In this review, previous studies concerning the GH secretory pattern in cattle, including its ultradian rhythm, are introduced and the regulatory mechanism is discussed on the basis of recent findings.

Key words: cattle, growth hormone, hypothalamus, ultradian rhythm.

INTRODUCTION

Growth hormone (GH) secreted from the anterior pituitary is recognized as one of the most important hormones for body growth in cattle (Etherton & Bauman 1998). In many species, GH is secreted from the somatotropes in the anterior pituitary in a pulsatile manner. The regularity of pulsatile secretion of GH was identified for the first time in male rats, with an approximately 3-h interval with constant amplitude (Tannenbaum & Martin 1976). This kind of rhythm showing less than 24-h interval is defined as ultradian rhythm. Clark and Robinson (1985) reported that GH-releasing hormone (GHRH) administration at similar intervals to the GH ultradian rhythm stimulated growth in normal and GHRH-deficient rats. This observation suggested that GH rhythm is one of the important factors modulating growth rate. Similar ultradian rhythm of GH secretion has been observed in male Shiba goats, albeit with a different time interval compared with that in rats (Mogi et al. 2002). We have reported that the GH ultradian rhythm is also found in Holstein steers (Kasuya et al. 2012). As clarified in rats, it is highly possible that the GH ultradian rhythm is important for maintaining body growth in these ruminants.

GH secretion is mainly controlled by the hypothalamic releasing (GHRH) and inhibiting (somatostatin; SS) hormones. In addition to this classic hypothalamic-pituitary axis, various neurotransmitters, neurohormones or peripheral factors, such as ghrelin, are reported to be regulatory factors of GH secretion (Muller et al. 1999; Khatib et al. 2014). The regulatory mechanism of the ultradian rhythm of GH secretion in the central nervous system has been studied in experimental animals (details will be described later in this review). Because there are species differences in the GH secretory pattern and regulation, it is necessary to gather scientific evidence in cattle to understand the GH axis in this species.

GH SECRETORY PATTERN IN CATTLE

The variations in the GH secretory pattern in cattle reported previously should be first discussed. The 24-h profile of GH secretion in cattle is relatively well established. Previous reports show that similar to other species, GH secretion is pulsatile in cattle. Plouzek and Trenkle (1991) reported a detailed intrabreed comparison of GH secretion in cattle. They determined the GH secretory profile at 5, 8, 12 and 15 months of age in crossbred bulls, steers, heifers and ovariectomized cows. They showed that GH is secreted in an irregular pulsatile manner with the highest amplitude in bulls and that plasma GH concentrations were decreased according to age. Lee et al. (1991) also reported that GH secretion is pulsatile with irregular pulses in Angus bulls and steers. Pulsatile GH secretion with irregular pulses has also been observed in heifers (Ozawa et al. 1991; Borromeo et al. 1994). In addition to these studies using growing
animals, Mollet and Malven (1982) reported that any regularity in GH secretion was not observed in lactating cows. Furthermore, a clear regularity of GH secretory pattern was not found in Mithuns, semi-wild type cattle (Mondal et al. 2004). The reports introduced above demonstrate the pulsatility of GH secretion in cattle, although no regularity of the secretion was observed. On the other hand, we recently observed that GH is secreted in a pulsatile manner with approximate 6-h intervals in Holstein steers under 12:12 L:D lighting conditions (Kasuya et al. 2012), and the pulse interval is similar to that in male goats (Mogi et al. 2002). Our observation was partly similar to the previous report of Angus steers in which the GH secretory pattern demonstrated regularity (Breier et al. 1986).

The exact reason for variations in the GH secretory pattern in this species is still unknown. One possible reason is the feeding regimen. Wheaton et al. (1986) suggested that synchronization of GH secretion observed in the afternoon may be caused by feeding. The effect of feeding on the synchronization of GH pulses has also been indicated in Holstein steers (Moseley et al. 1988). Wheaton et al. (1986) found that the mean concentrations of GH are kept at a low level subsequent to feeding. The feeding regimen that they used for maintaining a constant GH secretory pattern is suggested to be useful to determine the timing of exogenous drug application, such as dopamine or serotonin agonists, for evaluating their effects on GH secretion as suggested by other studies (Gaynor et al. 1995; McMahon et al. 1998). Breier et al. (1986) reported the relationship between the GH secretory pattern and nutritional status in steers. The distinct rhythm of GH secretion without synchronicity among animals was identified in medium and low dry matter levels of feeding but not in the high-level group.

Other candidates that may be responsible for determining the regularity of GH secretion appear to be environmental factors, particularly the lighting regimen. Recently, we found that the large peak of GH that usually appears around midnight (a part of the ultradian rhythm) was suppressed by 1-h light exposure starting at 00.00 hours (Kasuya et al. 2008a). Because the suppressed GH peak can be considered as part of the GH secretory rhythm in steers and was followed by an irregular peak, it is possible that photic stimulation during the dark period can disturb the regular GH ultradian rhythm. This inhibition of the GH peak by light was consistent with the observation in male rats (Davies et al. 2004). The study of male rats revealed that a photic signal stimulated SS release in the periventricular nucleus followed by GH suppression. Evans et al. (1991) reported that the photoperiod affects GH secretory rhythm in cows. Dopamine is suggested to be one of the central factors connecting light signals and GH secretion (Reuss et al. 1999). Dopamine is also considered to play an important role in the generation of a GH secretory rhythm (Díaz-Torga et al. 2002).

REGULATORY MECHANISM OF ULTRADIAN RHYTHM OF GH SECRETION

It is important to discuss the regulatory mechanism of the ultradian rhythm of GH secretion, because the rhythm appears to be an important factor for controlling body growth, as mentioned in the introduction section.

Since the first report on GH ultradian rhythm in male rats by Tannenbaum and Martin (1976), many studies have been conducted to elucidate the underlying regulatory mechanism. It has been suggested that GH secretion is controlled by two hypothalamic factors, GHRH and SS; thus, the relationships between GH secretory patterns and these two factors should be evaluated to understand the mechanism of GH ultradian rhythm generation. Furthermore, it is debatable as to which factor is more important in generating the ultradian rhythm of GH secretion. To determine the mechanisms underlying GH ultradian rhythm generation, the secretory patterns of both GHRH and SS were determined by direct approach to the central nervous system. It has been suggested that SS is involved in pulsatile GH release via a short-loop feedback system using the push-pull perfusion technique in rats (Kasting et al. 1981). However, the study by Kasting et al. (1981) was performed before the isolation of GHRH molecules by Guillemin et al. (1982). Therefore, determination of the role of GHRH in generating the GH rhythm was postponed to a future study. Plotsky and Vale (1985) determined that the GH secretory episodes were generated by GHRH release into the pituitary portal circulation accompanied by moderate SS reduction in anesthetized rats. In addition to the direct approach to their secretory profiles, the roles of GHRH and SS as leading players for the generation of GH pulses under physiological conditions were evaluated using indirect approaches, such as determination of the effects of their antisera on GH secretion.

Excellent studies have been conducted using Shiba goats to determine the important factors driving GH pulsatility using direct measurement of GHRH and SS concentrations in cerebrospinal fluid (CSF) from the third ventricle. Mogi et al. (2004) determined the secretory profiles of plasma GH, GHRH and SS in CSF in male goats in which a distinct ultradian rhythm of GH secretion was identified. This regularity of GH secretion was also observed in female goats and varied according to the estrus cycle (Yonezawa et al. 2005). The research regarding GH pulsatility using Shiba goats from this group also generated additional results suggesting that GH pulses are not related to GHRH and SS but have a negative correlation with neuropeptide Y (NPY) (Yonezawa et al. 2010). Furthermore, they also suggested that estrogen enhances the GH secretory pattern through stimulation of GHRH and suppression of NPY (Yonezawa et al. 2011). Although we attempted to determine the relationship between two hypothalamic hormones
secreted into the median eminence of the hypothalamus and peripheral GH using a push-pull perfusion system in Holstein steers, no obvious relationship among the three hormones was observed (Kasuya et al. 2005). However, Thomas et al. (2009) reported that GHRH concentration in CSF from the third ventricle was correlated with GH pulses. The correlation between the two hormones was weak, but over 50% of GH pulses were preceded by GHRH, and the majority of GHRH pulses were followed by GH within 20 min. Although SS concentrations were not measured in the report by Thomas et al. (2009), it is possible that GHRH plays a dominant role in the generation of GH pulses in cattle. They have also suggested that NPY injection into the third ventricle tends to induce GH secretion via the hypothalamus (Kasuya et al. 2006, 2008b) and frequent CSF sampling to measure the concentrations of neurotransmitters considered as regulators of GH secretion (Kasuya et al. 2010).

**PERSPECTIVES**

It is considered that the somatotropic axis (comprising the hypothalamus, pituitary GH and peripheral target organs) is important for the cattle industry, because GH plays an important role in not only body growth but also lactation. The ultradian rhythm of GH secretion has been observed in cattle, similar to that in other species. The rhythm is considered to be one of the important factors controlling body growth. However, little information is available regarding the regularity of GH secretion in cattle, and the underlying regulatory mechanism is as yet unknown. It remains to be determined whether sexual dimorphism exists in the rhythm, whether the rhythm appears at birth (or when it starts), and whether the rhythm is important for lactation or reproduction. In addition to the GH rhythm itself, it has been suggested that nutritional (internal) or environmental (external) factors have a strong effect on the rhythm. It is well known that the exogenous application of GH has positive effects on body growth and lactation. However, this technique or other hormonal applications to enhance GH secretion have not been accepted by consumers, at least not in Japan, because of fears for food safety. Information regarding the effects of nutritional and environmental factors on GH secretion may be a clue to solving the problem if we consider utilizing the "somatotropic axis" to improve cattle production. These factors are preferable because they can modify endogenous GH secretion without possible risks caused by exogenous hormones or drugs. The central nervous system is certainly the main regulator connecting these factors and the GH rhythm and should be investigated further. Physiological evidence obtained from fundamental observations of the GH secretory profile mostly focused on the pituitary and peripheral factors, in combination with the results obtained from newly applied neuroendocrinological studies, will provide us additional information for application in both animal physiology and husbandry in the future.

**ACKNOWLEDGMENTS**

This work was supported by Grants-in-Aid for Scientific Research (C) (19580333, 21580353, 25450403) from the Japan Society for the Promotion of Science. The author is grateful to Dr. Madoka Sutoh, National Institute of Livestock and Grassland Science, Japan, for her significant comments on this manuscript during preparation.
REFERENCES

Borromeo V, Cremonesi F, Perucchetti E, Berrini A, Secchi C. 1994. Circadian and circannual plasma secretory patterns of growth hormone and prolactin in freesian heifers: hormonal profiles and signal analysis. Comparative Biochemistry and Physiology 107A, 313–321.

Breier BH, Bass JJ, Butler JH, Gluckman PD. 1986. The somatotrophic axis in young steers: influence of nutritional status on pulsatile release of growth hormone and circulating concentrations of insulin-like growth factor 1. Journal of Endocrinology 111, 209–215.

Clark RG, Robinson ICAF. 1985. Growth induced by pulsatile infusion of an amidated fragment of human growth hormone releasing factor in normal and GHRF-deficient rats. Nature 314, 281–283.

Davies JS, Carter DA, Wells T. 2004. Photic stimulation inhibits growth hormone secretion in rats: a hypothalamic mechanism for transient entrainment. Endocrinology 145, 2950–2958.

Diaz-Torga G, Feierstein C, Libertun C, Gelman D, Kelly MA, Low MJ, et al. 2002. Disruption of the D2 dopamine receptor alters GH and IGF-I secretion and causes dwarfism in male mice. Endocrinology 143, 1270–1279.

Etherdon TD, Bauman DE. 1998. Biology of somatotropin in growth and lactation of domestic animals. Physiological Reviews 78, 745–761.

Evans NM, Hacker RR, Hoover J. 1991. Effect of chronobiological alteration of the circadian rhythm of porolactin and somatotropin release in the dairy cow. Journal of Dairy Science 74, 1821–1829.

Farhy LS, Veldhuis JD. 2004. Putative GH pulse renewal: periventricular somatostatinergic function of an arcuate-nuclear somatostatin and GH-releasing hormone oscillator. American Journal of Physiology: Regulatory, Integrative and Comparative Physiology 286, R1030–R1042.

Gaynor PJ, Lookingland KJ, Tucker HA. 1995. 5-hydroxytryptaminergic receptor-stimulated growth hormone secretion occurs independently of changes in peripheral somatostatin concentration. Proceedings of the Society for Experimental Biology and Medicine 209, 79–85.

Guillemin R, Brazeau P, Bohlen P, Esch F, Ling N, Wehrenberg WB. 1982. Growth hormone-releasing factor from a human pancreatic tumor that causes acromegaly. Science 218, 585–587.

Hashizume T, Kasuya E. 2009. Methodology for the study of the hypothalamic-pituitary hormone secretion in cattle. Animal Science Journal 80, 1–11.

Kasting NW, Martin JB, Arnold MA. 1981. Pulsatile somatostatin release from the median eminence of the unanesthetized rat and its relationship to plasma growth hormone levels. Endocrinology 109, 1739–1745.

Kasuya E, Kushiibiki S, Sutoh M, Saito T, Ito S, Yayou K, et al. 2006. Effect of melatonin injected into the third ventricle on growth hormone secretion in Holstein steers. Journal of Veterinary Medical Science 68, 1075–1080.

Kasuya E, Kushiibiki S, Yayou K, Hodate K, Ogino M, Sutoh M. 2012. The effect of lighting conditions on the rhythmicity of growth hormone secretion in Holstein steers. Animal Science Journal 83, 238–244.

Kasuya E, Kushiibiki S, Yayou K, Hodate K, Sutoh M. 2008a. Light exposure during night suppresses nocturnal increase in growth hormone secretion in Holstein steers. Journal of Animal Science 86, 1799–1807.

Kasuya E, Kushiibiki S, K-i Y, Ito S, Saito T, Hodate K, Sutoh M. 2008b. Effects of serotonin injected into the third ventricle on prolactin and growth hormone secretion in Holstein steers. Animal Science Journal 79, 362–367.

Kasuya E, Sakamoto R, Saito T, Ishikawa H, Sengoku H, Nemoto T, Hodate K. 2005. A novel stereotaxic approach to the hypothalamus for the use of push-pull perfusion cannula in Holstein calves. Journal of Neuroscience Methods 141, 115–124.

Kasuya E, Yayou K, Hashizume T, Kitagawa S, Sutoh M. 2010. A possible role of central serotonin in L-tryptophan-induced GH secretion in cattle. Animal Science Journal 81, 345–351.

Khatib N, Gaidhane S, Gaidhane AM, Khatib M, Simkhada P, Gode D, Zahiruddin QS. 2014. Ghrelin: ghrelin as a regulatory Peptide in growth hormone secretion. Journal of Clinical and Diagnostic Research 8, MC13–7.

Lee CY, Hunt DW, Gray SL, Henricks DM. 1991. Secretory patterns of growth hormone and insulin-like growth factor-I for 24 hours and after injection of bovine growth hormone-releasing factor into the hypothalamus for the use of push-pull perfusion cannula. Animal Science Journal 52, 2950–2958.

Morgan E, Chapin LT, Lookingland KJ, Tucker HA. 1998. Stimulation of dopamine D1 receptors increases activity of periventricular somatostatin neurons and suppresses concentrations of growth hormone. Domestic Animal Endocrinology 15, 257–265.

Mogi K, Li JY, Suzuki M, Sawasaki T, Takahashi M, Nishihara M. 2002. Characterization of GH pulsatility in male shiba goats: effects of post pubertal castration and KP102. Endocrine Journal 49, 145–151.

Mogi K, Yonezawa T, Chen DS, Li JY, Suzuki M, Yamanouchi K, et al. 2004. Relationship between growth hormone (GH) pulses in peripheral circulation and GH-releasing hormone and somatostatin porphyles in the cerebrospinal fluid of goats. Journal of Veterinary Medical Science 66, 1071–1078.

Mollet TA, Malven PV. 1982. Chronological profiles of prolactin and growth hormone in lactating cows. Journal of Dairy Science 65, 211–216.

Montal M, Dalhi A, Rajkhowa C, Prakash BS. 2004. Secretion Patterns of Growth Hormone in Growing Captive Mithuns (Bos frontalis). Zoological Science 21, 1125–1129.

Moseley WM, Alaniz GR, Claffin WH, Krabill LF. 1988. Food intake alters the serum growth hormone response to bovine growth hormone-releasing factor in meal-fed Holstein steers. Journal of Endocrinology 117, 253–259.

Muller EE, Locatelli V, Cocchi D. 1999. Neuroendocrine control of growth hormone secretion. Physiological Reviews 79, 511–607.

Ozawa A, Hodate K, Miyamoto S, Ohtani F, Tsushima T, Johke T. 1991. Plasma profile of insulin-like growth factor-I for 24 hours and after injection of bovine growth hormone in dairy heifers. Animal Science Technology (Japan) 62, 933–938.

Plotsky PM, Vale W. 1985. Patterns of growth hormone-releasing factor and somatostatin secretion into the hypophysial-portal circulation of the rat. Science 230, 461–463.

Plouzek CA, Trenkle A. 1991. Growth hormone parameters at four ages in intact and castrated male and female cattle. Domestic Animal Endocrinology 8, 63–72.

Reuss S, Hemes B, Fuchs E, Hiemke C. 1999. Day- and night-time blood concentrations of monoamines and their metabolites in the medial preoptic area of the rat hypothalamus. Neuroscience Letters 266, 29–32.
Saito T, Nemoto T, Nagase Y, Kasuya E, Sakumoto R. 2004. Development of a stereotaxic instrument for study of the bovine central nervous system. *Brain Research Bulletin* **62**, 369–377.

Tannenbaum GS, Martin JB. 1976. Evidence for an endogenous ultradian rhythm governing growth hormone secretion in the rat. *Endocrinology* **98**, 562–570.

Thomas MG, Amstalden M, Hallford DM, Silver GA, Garcia MD, Keisler DH, Williams GL. 2009. Dynamics of GHRH in third-ventricle cerebrospinal fluid of cattle: relationship with serum concentrations of GH and responses to appetite-regulating peptides. *Domestic Animal Endocrinology* **37**, 196–205.

Wagner C, Caplan SR, Tannenbaum GS. 1998. Genesis of the ultradian rhythm of GH secretion: a new model unifying experimental observations in rats. *American Journal of Physiology, Endocrinology and Metabolism* **38**, E1046–E1054.

Wheaton JE, Al-Raheem SN, Massri YG, Marcek JM. 1986. Twenty-four-hour growth hormone profiles in Angus steers. *Journal of Animal Science* **62**, 1267–1272.

Yonezawa T, Mogi K, Li JY, Sako R, Manabe N, Yamanouchi K, Nishihara M. 2010. Negative correlation between neuropeptide Y profile in the cerebrospinal fluid and growth hormone pulses in the peripheral circulation in goats. *Neuroendocrinology* **91**, 308–317.

Yonezawa T, Mogi K, Li JY, Sako R, Manabe N, Yamanouchi K, Nishihara M. 2011. Effects of estrogen on growth hormone pulsatility in peripheral blood and neuropeptide profiles in the cerebrospinal fluid of goats. *Journal of Reproduction and Development* **57**, 280–287.

Yonezawa T, Mogi K, Li JY, Sako R, Yamanouchi K, Nishihara M. 2005. Modulation of growth hormone pulsatility by sex steroids in female goats. *Endocrinology* **146**, 2736–2743.