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REVIEW ARTICLE

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 recoginized 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 intreval 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

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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 (Diaz-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 release and increases GHRH in CSF (Thomas *et al*. 2009). This observation suggests that NPY has a positive effect on the generation of GH pulses in cattle, and is inconsistent with a report using goats that outlined a negative correlation of NPY with GH pulses (Yonezawa *et al*. 2010).

In addition to the evidence from neuroendocrine experiments, the regulatory mechanism of the GH ultradian rhythm has also been discussed using mathematical models. Wagner *et al*. (1998) simulated the mechanism underlying the generation of the 3.3-h ultradian rhythm of GH secretion in male rats; they explained the mechanism, as described below. In basic terms, GH is secreted by 1-h interval GHRH pulses. However, the secreted GH inhibits its own secretion via GH receptors on SS neurons. SS released from the hypothalamus delays the process for approximately 1 h and maintains a high level for over 1 h. They suggested that the 3.3-h interval of GH secretion in male rats is the result of this combination of intrinsic GHRH-GH secretion and SS secretion. In addition, Farhy and Veldhuis (2004) demonstrated the concept of a network model for generating the GH rhythm in male rodents.

Currently, the evidence for the regulatory mechanism of the GH secretory pattern is mostly supported by experiments using experimental model animals. However, as mentioned in this review, the GH secretory pattern demonstrates interspecies variation. Therefore, it is necessary to utilize cattle to eventually understand the specific system of GH secretion in this species. Several laboratories, including our own, have attempted to measure concentrations of hypothalamic hormones controlling pituitary hormone secretion in cattle, as described above; however, it is a challenge to apply a neuroendocrinological experimental technique *in vivo*. The difficulty of this application is mainly the result of the large body size of the animal. We have developed a stereotaxic apparatus designed for cattle (Saito *et al*. 2004) enabling us to approach a specific brain area, in particular the hypothalamus and its vicinities (Hashizume & Kasuya 2009). The technique is useful for the experiments described below: push-pull perfusion in the median eminence to measure the concentrations of GHRH and SS (Kasuya *et al*. 2005), intraventricular injection of various candidates playing an important role in the regulation of GH secretion to evaluate their effects on 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.

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