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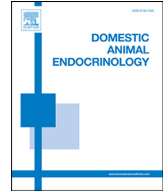

Ovarian and hormonal responses to single or continuous peripheral administration of senktide, a neurokinin 3 receptor agonist, during the follicular phase in goats

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ABSTRACT

The present study aimed to investigate the effects of single or continuous administration of a neurokinin 3 receptor agonist, senktide, on hormonal and follicular dynamics in follicular phase goats. Goats were injected with $PGF_{2\alpha}$ in the luteal phase and treated with an intravaginal progesterone device for 10 d. At 12 h after the cessation of progesterone treatment, the goats received a single intravenous injection of senktide (200 nmol, n = 4) or vehicle (n = 4), or continuous intravenous infusion of senktide (20 nmol/min, n = 6) or vehicle (n = 6) for 6 h. Blood sampling and ovarian ultrasonography were performed during the experiment. A single injection of senktide did not influence the number of luteinizing hormone (LH) pulses and mean LH concentration. On the other hand, continuous injection of senktide caused a sustained increase in LH secretion, and mean LH concentration in samples collected at 10-min intervals for 6 h after the start of infusion was higher than that of vehicle-treated goats (2.8 ± 1.3 vs 1.0 ± 0.6 ng/mL, $P < 0.01$). In 4 of 6 goats, LH concentrations reached their peaks during the 6-h senktide infusion, and ovulation was observed at 48 h after the start of infusion without estrous behavior. The remaining 2 senktide-treated goats and all vehicle-treated goats showed estrus and ovulated at 72 or 96 h after treatment. These results suggest that continuous infusion of senktide in follicular phase goats can cause a sustained increase in LH and advance the time of ovulation.

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1. Introduction

For most mammalian species, gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH) are important endocrine regulators for maintaining normal ovarian function, including follicular development, steroidogenesis, and ovulation. Accumulating evidence suggests that kisspeptin neurons play a key role in the regulation of GnRH/LH secretion [1]. Furthermore, it has been found that most of the kisspeptin neurons in the arcuate nucleus (ARC) coexpress neurokinin B (NKB) and dynorphin A in mice [2], as well as in sheep [3] and goats [4].

NKB is a member of the tachykinin family of peptides. NKB and its receptor, neurokinin 3 (NK3R), are found to be distributed in both the central and peripheral nervous systems [5]. Since the discovery of NKB [6,7], researchers have been focusing on the functional roles of this peptide in the nervous system. Recently, loss-of-function mutations of *Tac3* and *Tacr3* genes, which encode NKB and NK3R, respectively, have been identified in patients with hypogonadotropic hypogonadism [8,9]. Young et al [10] demonstrated that pulsatile GnRH administration to patients with TAC3 and TACR3 mutations restores pulsatile LH secretion and gonadal function. Moreover, administration of

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NKB stimulates LH release in monkeys [11], rodents [12], sheep [13,14], and goats [4]. This evidence suggests that NKB and NK3R signaling has a crucial role in reproductive function via the regulation of hypothalamic GnRH secretion.

Given the importance of NKB/NK3R signaling in reproductive function, the clinical application of NKB or its analog may have a potential benefit for patients with sterility due to insufficient gonadotropin secretion. Senktide is a synthetic peptide and a highly selective agonist of NK3R [15]. In addition, senktide also has much higher metabolic stability than native tachykinins, making it a useful experimental tool [16].

Recently, we examined the therapeutic effects of senktide on goats that were clinically diagnosed as anestrus [17]. In that study, a single peripheral injection of senktide elicited an immediate increase in LH secretion similar to that released spontaneously in follicular phase goats, and the induced LH secretion by repetitive injections of senktide at 4-h intervals for 24 h promoted follicular development and ovulation [17]. However, there is still insufficient information to evaluate hormonal and follicular responses to continuous senktide treatment in cycling animals. Contradictory results regarding the effects of continuous infusion of senktide on LH secretion have been reported between intact and ovariectomized animals. Central infusion of senktide stimulated LH secretion in follicular phase and anestrous ewes [13], whereas no significant effect of peripheral senktide infusion on LH secretion was found in ovariectomized goats [18].

Therefore, the objective of the present study was to examine the effects of single or continuous administration of senktide on LH secretion during follicular phase in goats and their association with circulating estradiol concentrations, follicular dynamics, and occurrence of estrus.

2. Materials and methods

2.1. Animals

Thirteen adult cycling Shiba goats (4.1 ± 2.6 [mean ± standard deviation] yr of age; 23.9 ± 4.8 kg of body weights) maintained at the Tokyo University of Agriculture and Technology were used. Shiba goats are annual breeders under natural daylight conditions in Japan and have been used as an experimental model for domestic ruminants. The goats were housed in outdoor paddocks with sheltered areas and were fed maintenance diets of alfalfa hay cubes (350 g) twice a day. Clean water and mineralized salt were available ad libitum. All goats were confirmed to be clinically healthy and in good condition, and to have normal estrous cyclicity before being submitted to the study. All procedures were approved by the University Committee for the Use and Care of Animals at Tokyo University of Agriculture and Technology (no. 22–67).

2.2. Experimental protocol

2.2.1. Effects of single injection of senktide on LH secretion in follicular phase goats

The experiment was conducted during the period between August and November in 2013. Four goats each received a single intravenous injection of senktide (200 nmol in 5 mL of saline containing 0.25% dimethyl sulfoxide) or vehicle using a crossover design. At least 1 estrous cycle was allowed to elapse between the 2 treatments. The dose of senktide was determined based on our pilot study, in which the dose was found to be effective in inducing a pulsatile increase in LH secretion in anestrous goats [17]. They were checked for estrus daily, and ovaries were monitored by ultrasonography to determine the day of ovulation. At 7 to 14 d after ovulation, all goats were injected with $PGF_{2\alpha}$ (2 mg of dinoprost, Pfizer, Tokyo, Japan) to induce luteolysis. They were then treated with intravaginal progesterone-releasing devices containing 0.3 g of progesterone (CIDR: CIDR-G; Pfizer New Zealand, Auckland, New Zealand) for 10 d. At 12 h after CIDR removal, goats received a single injection of senktide or vehicle. Blood samples (2 mL) were collected every 10 min from −2 to 6 h after injection for the determination of plasma LH. A catheter (18 gauge, 30-cm length; Medicut Catheter Kit, Sherwood Co, Tokyo, Japan) was inserted into the jugular vein before the start of blood collection. Blood samples were centrifuged at 1,750 × g for 20 min at 4°C, and the plasma was stored at −20°C until assay.

Development of follicles was monitored daily by ovarian ultrasonography, starting on the day before senktide treatment until the detection of ovulation. After ovulation, ultrasound examinations and blood sampling were performed every other day during the luteal phase, and then daily after the start of luteal regression until the subsequent ovulation.

2.2.2. Effects of continuous infusion of senktide on LH secretion, estrus, and ovulation in follicular phase goats

The experiment was conducted on 12 goats during the period between September and December in 2014. Pretreatment with $PGF_{2\alpha}$ and CIDR was conducted in the same manner as the first experiment. At 12 h after CIDR removal, the goats received a continuous infusion of senktide (20 nmol/min, n = 6) or vehicle (saline containing 0.25% dimethyl sulfoxide, n = 6) for 6 h via a catheter inserted into the jugular vein. Blood samples (2 mL) were collected from another catheter inserted into the opposite jugular vein every 10 min from −2 to 6 h for the determination of plasma LH. During this period, goats were kept in individual pens. After finishing infusion, the catheters were withdrawn and goats were returned to the paddocks, and blood samples were collected by jugular venipuncture every 6 h from 6 to 48 h, and at 72 and 96 h after the start of infusion. In addition, occurrence of estrus was checked by using male goats at each time of blood sampling, starting at 6 h after the start of infusion. The obtained samples were centrifuged at 1,750 × g for 20 min at 4°C, and plasma was stored at −20°C until assay. The samples collected hourly from −2 to 6 h, every 6 h from 0 to 48 h, and at 72 and 96 h after the start of infusion were used for the determination of plasma estradiol.

2.3. Ovarian ultrasonography

Ovarian ultrasonography was performed in both experiments, basically on the day of CIDR insertion and

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