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Induction of ovulation in anestrus ewes using a dopamine receptor antagonist

Vijay Kumar Saxena^{a,b,*}, Kalyan De^a, Davendra Kumar^a,
Syed Mohammad Khurshheed Naqvi^a, Narayanan Krishnaswamy^c,
Ashok Kumar Tiwari^b

^a Molecular Physiology Laboratory, Division of Animal Physiology and Biochemistry, ICAR-Central Sheep and Wool Research Institute, Avikanagar, India

^b Division of Animal Biotechnology, ICAR-Indian Veterinary Research Institute, Izatnagar, India

^c Division of Animal Reproduction, ICAR-Indian Veterinary Research Institute, Izatnagar, India

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ABSTRACT

Estradiol decreases the pulse frequency of LH during the nonbreeding season through dopaminergic neurons that results in anestrus in the ewe. Long-term administration of sulpiride, a dopamine antagonist, induced ovulation in seasonally anestrus mares. Accordingly, we tested whether sulpiride would induce ovulatory estrus in seasonally anestrus Malpura ewes. A total of 12 Malpura ewes were divided into sulpiride (at 0.6 mg/kg *b.i.d.*) or control groups. Anestrus was defined on the basis of the absence of heat signs for 2 months through twice-a-day heat detection during the nonbreeding season (October–November) and progesterone level of less than 1 ng/mL. Rates of estrus induction, ovulation, multiple ovulations, and lambing in the sulpiride-treated ewes were 83.3%, 100%, 16.6%, and 66.7%, respectively. The mean interval from treatment to estrus was 5.25 ± 1.49 days. Progesterone levels were elevated after ovulation significantly on Days 5 and 7 after estrus as compared to Day 0 after sulpiride treatment ($P < 0.05$). In contrast, none of the control group ewes showed either estrus or ovulation. There was a significant association between sulpiride treatment and estrus induction rate as well as ovulation rate ($P < 0.05$). It is concluded that the result provides proof of concept that the dopamine antagonist can induce ovulation in seasonally anestrus ewes.

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1. Introduction

Seasonal anestrus, which is controlled by the photoperiod in temperate sheep, limits the ability of achieving the global target of three lambs per ewe every 2 years. In contrast, nutritional and environmental cues decide the breeding season in the tropical or subtropical ewes [1]. Ewes in seasonal anestrus have lower circulating levels of LH, FSH, and estradiol with basal levels of progesterone [2,3]. As in cattle, follicles grow and regress in a wave-like

fashion during anestrus with steroidogenic capacity [4,5]. A distinct decrease in the LH pulse frequency is the hallmark endocrine feature of ewes during seasonal anestrus [6] which is imputed to two major inhibitory mechanisms: (1) the hypothalamus is highly sensitive to the inhibitory effects of estradiol on LH release, even at low concentrations and (2) a direct inhibitory effect of long photoperiod on the hypothalamo–hypophyseal axis [7].

Integrated dopaminergic circuits at the hypothalamus are reported to mediate the enhanced sensitivity of estradiol negative feedback on LH release during seasonal anestrus [8]. In particular, A15 dopaminergic neurons in the retrochiasmatic area reduce the LH pulse frequency in response to estradiol [9,10] through the D2 dopamine

* Corresponding author. Tel.: +91 1437 220165; fax: +91 1437 220163.
E-mail address: drvijaysaxena@gmail.com (V.K. Saxena).

receptors [11,12]. Surprisingly, immunolocalization studies failed to demonstrate the presence of estrogen receptors in A15 neurons. However, estrogen-responsive afferents are present in the ventromedial preoptic area and retrochiasmatic area [13]. Goodman et al. [14] reported that the dopamine neurons check the GnRH pulse frequency by suppressing the activity of kisspeptin (Kiss) neurons in the arcuate nucleus which are essential for the onset of puberty and transition from nonbreeding to breeding season [15,16]. During the anestrus period, the expression of Kiss1 receptor [17] and the connectivity of Kiss neurons to GnRH neurons decrease [18]. Recently, Goodman et al. [14] reported that A15 neurons synapse at arcuate nucleus and suppress the activity of Kiss neurons to inhibit GnRH pulses during anestrus. In parallel, dopamine receptor (D2R) expression is doubled on Kiss neurons during seasonal anestrus as compared to the breeding season. On the basis of the aforementioned observations, we hypothesized that administration of a dopamine antagonist would induce ovulation in seasonally anestrus Malpura ewes. Sulpiride is a substituted benzamide with selective dopaminergic blocking activity. Sulpiride in humans is generally used as an antipsychotic drug in the management of the symptoms of schizophrenia. At low dosages (50–150 mg/day) in humans, sulpiride produces a disinhibiting and antidepressant effect by its action on D2 presynaptic autoreceptors, thus facilitating dopaminergic neurotransmission [19]. Sulpiride was preferred over domperidone as a dopamine antagonist because the former drug crosses the blood–brain barrier [20]. The dose of sulpiride was chosen on the basis of its reported effectiveness without any apparent toxicologic complications in stimulating pulsatile secretion of LH in Soay rams in earlier studies [21,22]. Besognet et al. [23] too investigated the role of the dopamine antagonist in the regulation of seasonal reproductive activity in mares and found that the use of sulpiride at the dose of 200 mg/animal was able to hasten the first ovulation of the year. Mean day of first ovulation was significantly advanced for sulpiride-treated mares (77 days) than for control mares (110 days) in their study. An increase in LH secretion in anestrus primiparous cows was observed after the administration of the dopamine antagonist, metoclopramide [24].

Anestrus in ewes is one of the most important problems which limit the reproductive efficiency in the ewe. Attempts to breed ewes during anestrus through ram effect was not successful owing to their dependence on both the ram and ewe-associated factors such as sexual activity of ewes and rams, lactational status of ewes, and nutritional status [25]. At present, progesterone-releasing devices or implants, which mimic the hormonal pattern of a natural estrus cycle, are used to induce estrus in ewes during the nonbreeding season [26]. Melatonin implants have also been used to induce estrus in anestrus ewes [27], hasten the breeding season [28], or increase the conception rate [29]. However, controlled-release formulations of progesterone or melatonin are neither economical nor freely available in developing countries such as India. It behooves that developing novel strategies to induce estrus in seasonally breeding ewes is an interesting area of research. Accordingly, we tested the hypothesis whether the

dopamine antagonist could induce ovulation in seasonally anestrus Malpura ewes because estradiol reduces the LH pulse frequency in anestrus ewes through dopamine neurons [30].

2. Materials and methods

2.1. Experimental animals

The study was conducted on Malpura breed of ewes during the nonbreeding season (October–December) at the Central Sheep and Wool Research Institute, Avikanagar, Rajasthan, India, which is located 26.1633°N and 75.7869°E. The experiment was approved by the Animal Ethics Committee of the Central Sheep and Wool Research Institute, Avikanagar. Malpura ewes are atypical seasonal breeders with major reproductive activity during mid-March to April and mid-July to September, of which, the latter is the major breeding season with more than 80% tupping rate [31]. The ewes were maintained under grazing on natural pasture with supplementation of a concentrate feed. The flock was vaccinated against foot and mouth disease and peste des petits ruminants as per the prophylactic calendar. After the end of breeding season 2013, heat detection was done twice a day using an aproned ram on the barren ewes for 2 months and progesterone level was estimated at weekly interval to confirm anestrus. The ewes that failed to show estrus coupled with progesterone level of less than 1 ng/mL were considered as anestrus ewes ($n = 12$). The experimental ewes were in 2 to 4 years with a mean body weight of 35.5 kg. Ewes were in the first or second parity.

2.2. Experimental procedure

Seasonally anestrus Malpura ewes ($n = 12$) were divided into either one of the two groups: the treatment group received the dopamine antagonist, sulpiride (Sigma–Aldrich, St. Louis, MO, USA) at the rate of 0.6 mg/kg subcutaneously twice a day (morning 7 AM and evening 5 PM) till the onset of estrus, whereas the control ewes received an equal volume of normal saline. Sulpiride was diluted in 0.1-M tartaric acid in saline solution to achieve a final concentration of 100 mg/mL. Blood samples were collected daily till the onset of estrus and on Days 3, 5, and 7 after estrus. Heat detection was done twice a day (8 AM and 4 PM; 20 min/detection) using an aproned ram of proven fertility. Typical estrus signs such as frequent wagging of the tail and urination, ram-seeking behavior, and stands to be mounted are hallmarks of estrous behavior in ewes. Estrus ewes were mated with an elite ram as per the breeding plan. Estrus induction rate, interval between treatment and estrus, ovulation rate, and lambing rate were recorded. Observation on the control was limited to five as one ewe died during the study period.

2.3. Progesterone estimation

Blood samples were collected on Days 0, 3, 5, and 7 after estrus (Day 0 = estrus) to determine progesterone concentration. Plasma progesterone was estimated using

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