Domestic Animal Endocrinology 59 (2017) 116–133

Contents lists available at ScienceDirect

Domestic Animal Endocrinology

journal homepage: www.domesticanimalendo.com

Systemic and intrafollicular components of follicle selection in mares

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ARTICLE INFO

Article history:
Received 20 October 2016
Received in revised form 6 December 2016
Accepted 10 December 2016

Keywords:
Dominant follicle
Follicle deviation
Follicle selection
IGF
Mare
Subordinate follicle

ABSTRACT

Mares are superb models for study of follicle selection owing to similarities between mares and women in relative follicle diameters at specific events during the follicular wave and follicle accessibility for experimental sampling and manipulation. Usually, only 1 major follicular wave with a dominant follicle (DF) greater than 30 mm develops during the 22 to 24 d of the equine estrous cycle and is termed the primary or ovulatory wave. A major secondary wave occasionally (25%) develops early in the cycle. Follicles of the primary wave emerge at 6 mm on day 10 or 11 (day 0 = ovulation). The 2 largest follicles begin to deviate in diameter on day 16 when the future DF and largest subordinate follicle (SF) are 23 mm and 20 mm, respectively. The deviation process begins the day before diameter deviation as indicated in the future DF but not in the future SF by (1) increase in prominence of an anechoic layer and vascular perfusion of the wall and (2) increase in follicular-fluid concentrations of IGF1, vascular endothelial growth factor, estradiol, and inhibin-A. A systemic component of the deviation process is represented by suppression of circulating FSH from secretion of inhibin and estradiol from the developing DF. Production of inhibin is stimulated by IGF1 and LH, and estradiol is stimulated by LH and not by IGF1 in mares. A local intrafollicular component involves the production of IGF1, which apparently increases the responsiveness of the future DF to FSH. The roles of the IGF system have been well studied in mares, but the effect of IGF1 on increasing the sensitivity of the follicle cells to FSH is based primarily on studies in other species. The greater response of the future DF than the SF to the low concentrations of FSH is the essence of selection. During the common growth phase that precedes deviation, diameter of the 2 largest follicles increases in parallel on average when normalized to emergence or retrospectively to deviation. Study of individual waves indicates that (1) the 2 follicles change ranks (relative diameters) during the common growth phase in about 30% of primary waves and (2) after ablation of 1, 2, or 3 of the largest follicles at the expected beginning of deviation, the next largest retained follicle becomes the DF indicating that several follicles have the capacity for dominance; therefore, it is proposed that the deviation process represents the entire mechanism of follicle selection in mares.

1. Introduction

In mares, the ovulatory season in the northern temperate zone extends from about April to October, the length of the interovulatory interval (IOI) is about 22 d (horses) and 24 d (ponies), and ovulation occurs from a large follicle (eg, 40 mm) near the end of a long estrus (eg, 6 d) [1]. One or 2 follicular waves occur during an IOI, and each consists of many follicles (eg, 10) that reach greater than 6 mm in diameter. The ovulatory wave develops 13-mm follicles by day 10 or 11 (day 0 = ovulation) at the

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http://dx.doi.org/10.1016/j.domaniend.2016.12.005

peak of the wave-stimulating FSH surge. The 2 largest follicles grow approximately in parallel (common growth phase) until day 15 or 16 when the 2 largest follicles are a mean of 23- and 20-mm, and the FSH surge is declining [2]. At the end of the common growth phase, follicle deviation begins and is characterized by continued growth of the largest follicle to become the dominant follicle (DF) and the beginning of slower growth rate of the second largest follicle to become the largest subordinate follicle (SF). During deviation, the follicle destined to ovulate must escape a degenerative process (atresia), which affects the contemporaries of the wave. The DF of the last wave of an IOI becomes the ovulatory follicle.

In heifers, the process of deviation begins about 12 h before the manifestation of diameter deviation and involves an increase in granulosa LH receptors and estradiol-17β (estradiol) and maintenance of intrafollicular free IGF1 in the future DF (review [3]). Thereby, the future DF is developmentally prepared to use the declining FSH in the wave-stimulating FSH surge. A follicle that emerges first may maintain the largest diameter ranking and become the DF by being first to reach a critical developmental stage. However, the early size advantage is not a requisite component of the deviation process in heifers as indicated by (1) occasional switching in follicle diameter rankings during the common growth phase owing to intraovarian factors that affect growth of individual follicles, (2) a follicle that reaches 5 mm regardless of diameter ranking will become a DF unless it is selected against during deviation, and (3) a follicle is not developmentally prepared to become a DF until it is larger than 7.0 mm. It has been proposed that the mechanisms that underlie deviation and begin 12 h before the diameter manifestation of deviation fully represent the theory of follicle selection in cattle [3].

The biological selection of the DF or ovulatory follicle from a wave of many follicles in monovulatory species (cattle, horses, and humans) has been the subject of hundreds of reports during more than 5 decades (reviews that include mares [1,4–10]). Comparisons and contrasts of follicle selection or the deviation mechanism between mares and women are also available [11–13]. The present review is a history of published research results on follicle selection in mares before and after the introduction of transrectal ultrasonic imaging for the study of follicle dynamics [14]. A purpose of the review is to examine whether the deviation process may represent the entire follicle selection mechanism in mares as proposed for heifers [3].

2. Chronology of research studies on follicle selection in mares

A 90-yr history (1926–2016) on observations and research findings that contributed to our knowledge on the mechanisms that underlie the follicle selection process in mares is listed (Table 1). After an original observation in 1926, the number of reports increased gradually during 1972 to 2001 followed by many reports in 2002 to 2004 and a gradual decrease in 2005 to 2016. The progress was disjointed as expected owing at least partly to diverse interests and in the availability of instrumentation and expertize. Perhaps, the most salient milestones in research progress on follicle selection in mares were the introduction of an FSH assay and transrectal ultrasonic imaging and development of the concept of follicle deviation. Deviation or the dissociation in diameters of the 2 largest follicles was discovered in 1997, during the study of diameter graphs of each of the 2 largest follicles in individual waves. The growth rate of the future DF and the future SF changed relatively abruptly and served as a manifestation of selection as represented by the point of departure in changing diameters between the future DF and SF. The observation of diameter deviation allowed focusing on a specific event as a reference point or end point for studies on follicle selection. The influx of reports in 2002 to 2004 was related to (1) the development of transvaginal ultrasound techniques for sampling or injecting into a specific follicle including later sampling or determining whether the follicle became a DF or SF, (2) transrectal color Doppler ultrasound for assessing ovarian and follicular blood flow, and (3) the use of experimental deviation to compare time lines among systemic and intrafollicular factors.

3. Reports on selection before availability of ultrasonic imaging

Before the availability of ultrasonic imaging, sequential monitoring of follicle diameters throughout the IOI in mares was done by transrectal digital palpation. On the basis of palpation, it was reported in 1926 that several follicles of 20 to 30 mm are present before estrus, but during estrus, only 1 or 2 chosen follicles increase in diameter to an average of 50 mm [15]. The observation was subsequently confirmed [61]. Although the term follicle selection was not used, the phenomenon has been known in mares for at least 90 yr. A palpation study in 1972 noted that the follicle that was the largest on the first day of estrus (mean length, 7.7 d) remained largest and became the ovulatory follicle in 15 of 24 (62%) mares [16]. Daily monitoring by palpation throughout the IOI in 14 pony mares in 1979 indicated that the number of follicles greater than 20 mm did not increase significantly until after Day 10 [24]. The number of 20-mm follicles began to decrease on Day −7 or on the first day that the preovulatory follicle was the only follicle to increase in diameter (Fig. 1) [24]. In another palpation study, the preovulatory follicle became the largest follicle on the first or second day of estrus in 64% and 20%, respectively, of 56 estrous cycles or on a mean of 5.7 d before ovulation [24]. Although these findings were described before the availability of ultrasonic imaging, they provided the first indications that selection of the preovulatory follicle in mares is manifested by diameter dissociation between the largest follicle and other follicles beginning about 7 d before ovulation.

4. Transrectal and transvaginal ultrasonic imaging

The use of transrectal ultrasonic imaging for research in reproduction in large animals has been reviewed [62]. The first study on transrectal ultrasonic monitoring of reproductive structures in any species was done in mares and was reported in 1980 [25]. The ultrasound instrument at that time had relatively low transducer frequency