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Review Article

Prolactin in the Horse: Historical Perspective, Actions and Reactions, and Its Role in Reproduction

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ABSTRACT

Prolactin is a hormone with diverse biological effects in various species. The secretion of prolactin in horses is affected by season, thyrotropin-releasing hormone, dopaminergic and antidopaminergic agents, exercise and stressful stimuli, meal feeding, estrogen treatment, and antiopioidergic agents. The need of prolactin for mammary growth and lactation in mares has been elucidated from research on endophyte-infected fescue grazing and its associated problems in late gestation. This has led to the development of treatments for fescue toxicity and protocols for inducing lactation in nonpregnant mares. Treatment with prolactin has demonstrated that it is involved with the shedding of the winter coat in spring (increasing concentrations) and likely with the growth of the winter coat in the fall (decreasing concentrations). Prolactin secretion is highly correlated with the photoperiod and is low in winter and high in summer. The coincidence of rising prolactin concentrations in blood with the onset of ovarian activity during the spring transition period in mares led to research showing that prolactin treatment, or inducement of high prolactin secretion by means of antidopaminergic agents, in winter can induce ovarian activity and ovulation in seasonally anovulatory mares. The combination of a small amount of estrogen in addition to an antidopaminergic agent has been shown to produce a synergy resulting in very high prolactin concentrations in blood. The results of 39 years of research on equine prolactin illustrate nicely how the gradual accumulation of knowledge derived from basic research questions can generate applied solutions to real-world problems.

1. Historical Perspective—Discovery, Description, and Functional Variabilities Among Species

Prolactin in the horse is a 199-amino acid peptide hormone produced and secreted by the equine adenohypophysis (glandular portion of the pituitary). Stricker and Grueter [1], in 1928, first described the stimulatory activity of extracts of bovine adenohypophyses on rabbit mammary glands, and in 1933, Riddle et al [2] reported the stimulation of pigeon crop sacs by a substance in similar extracts and coined the term “prolactin” due to its milk-inducing effects.

Equine prolactin was first isolated and partially characterized by Chen et al [3] in 1979 and further in 1983 by Li and Chung [4]. Li and Chung [4] suggested that equine prolactin differs from that of other farm species in that it is one amino acid longer and contains only four cysteine residues rather than six common in other species, due to its lack of an NH_2-terminal disulfide loop [4]. More recently, Lehrman et al [5] reported that equine prolactin contained the typical six cysteine residues rather than four. The amino acid sequence, which contributes significantly to its immunologic (antigenic) properties, of equine prolactin is most similar (homologous) to canine (94%), porcine (93%),

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and fin whale (91%) prolactin compared with the human (78%), bovine (76%), ovine (75%), or mouse (57%) hormones [5–7]. In an immunocytochemical study, Rahmanian et al [8] reported that prolactin could be localized to two specific lactotrope types in equine adenohypophyseal tissue (types I and II, distinguished by size and secretion granule size and distribution). Lactotropes comprised between 5% and 16% of the cells in the gland. Prolactin was also found to colocalize with growth hormone in cells commonly referred to as mammosomatotropes, and these comprised an average of 6% to 16% of all cell types.

Extrapituitary sources of prolactin have been suggested in other species, and King et al [9], using immunocytochemical techniques, reported a localization of prolactin in the equine ovary in antral follicles, the ovulation fossa, and the corpus luteum. Moreover, they were also able to detect preprolactin cDNA in samples of follicular and luteal tissue, suggesting a potential for prolactin production in those tissues.

Prolactin is somewhat unique among pituitary hormones in its degree of variability of biological effects across species. Prolactin has been implicated in areas as diverse as growth of tadpoles and metamorphosis into frogs, luteal function and spermatogenesis in rodents, osmotic regulation in teleost fishes, modulation of immune system cells in various species, parenting and migration behaviors in birds and mammals, molting and regrowth of hair in winter foxes, and establishment of embryonic diapause in marsupials [10]. Thus, students of endocrinology, if asked “What does prolactin do?” must first ask in response “In what species?” obligatory effects of prolactin in one species, for example, its requirement for normal luteal function in the ewe [11], will not necessarily hold true in a different species. Given this diversity, the focus of this review will hereafter be on characteristics of prolactin, factors affecting its secretion, and its documented effects on physiological functions specifically derived from research on horses.

2. Measurement and Secretory Patterns

2.1. Measurement

The earliest publications concerning equine prolactin, based on the U.S. National Library of Medicine database, appeared in the 23rd Supplement of the Journal of Reproduction and Fertility as a result of presentations by Dr. Terry Nett at the First International Symposium on Equine Reproduction in Cambridge, UK, in July of 1974 [12]. Prolactin concentrations were described as high and variable for pregnant and postpartum mares, although the specifics of the assay (antiserum and iodinated preparation) were not given in the manuscript. It was not until 10 years later that Roser et al [13] developed and reported on a homologous radioimmunoassay (RIA) for equine prolactin. This opened the doors for research into equine prolactin, which blossomed thereafter. In 1986, Worthy et al [14] also reported data for prolactin in pregnant and postpartum pony mares, based on a homologous RIA, and the results were very similar to those of Nett et al [12]. Also in 1986, Thompson et al [15] reported on the use of an equine–canine RIA to measure equine prolactin. Subsequently, in 1991, that group developed and validated an RIA based on antiserum against porcine prolactin that they have used in all subsequent research [16]. Although variant in components, the various assays for equine prolactin have provided fairly consistent and biologically logical results across the numerous laboratories, with the exception of two reports [17,18], in which it was reported that thyrotropin-releasing hormone (TRH) did not affect prolactin secretion.

2.2. Secretory Pattern

Prolactin concentrations in horses at rest are relatively constant over time, except for occasional irregular pulses or episodes superimposed on the basal concentrations. Roser et al [19] described the episodic release of prolactin in cyclic mares at the same meeting where Worthy et al [20] reported occasional high prolactin concentrations in mares when secretion seemed otherwise basal. Thompson et al [21] measured prolactin in plasma samples drawn every 15 minutes from four mares housed indoors and reported that, superimposed over a declining baseline, there occurred 0, 1, 3, and 3 peaks, or surges, in prolactin in the 8-hour period. In contrast to those in the nonpregnant mare, Nett et al [22] reported that prolactin concentrations in mares during gestation were extremely variable with no clear pattern of fluctuation. Similarly, Cahill et al [23] described prolactin concentrations in lactating mares as having long episodic bursts, whereas Worthy et al [20] described them as high and irregular.

One situation where episodes in prolactin secretion seem to occur consistently is in late diestrus and the periovulatory period. Worthy et al [20] first described a marked rise in prolactin concentrations shortly before the onset of estrus in mares during fall estrous cycles, although this rise was less obvious in cycles in spring and summer. Irvine et al [24] reported a similar rise in prolactin associated with luteolysis in mares in autumn transition, and the occurrence was the same for ovulatory and nonovulatory cycles. Shand et al [25] induced luteolysis with prostaglandin-$F_{2\alpha}$ ($PGF_{2\alpha}$) and reported similar pulses in prolactin that occurred first around the time of the nadir of progesterone concentrations. King et al [26] also reported higher plasma prolactin concentrations in mares from 1 day before to 1 day after ovulation relative to the other days in the rest of the estrous cycle. Moreover, they reported follicular fluid prolactin concentrations of similar magnitude [26]. Ginther and Beg [27] looked at the prolactin response relative to the first naturally occurring $PGF_{2\alpha}$ metabolite peak during luteolysis and found it to be on the ascending side of that peak. Subsequently, Ginther et al [28] suggested that the pulses in prolactin occurring around the time of luteolysis were in fact driven by the pulses in $PGF_{2\alpha}$ occurring at that time, as opposed to the other way around.

Although endogenous pulses of prolactin occur around the time of luteolysis, their possible effects on luteolysis or ovulation are unknown. Becker and Johnson [29] first tested the hypothesis that prolonged hyperprolactinemia might affect the timing of ovulation or corpus luteum formation in mares. Hyperprolactinemia was produced with frequent metoclopramide injections either on day 17 (follicular phase) or 11 (diestrus). Treatment increased