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Domestic Animal Endocrinology 43 (2012) 154–160

DOMESTIC ANIMAL ENDOCRINOLOGY

www.domesticanimalendo.com

New developments on the galactopoietic role of prolactin in dairy ruminants

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Received 28 September 2011; received in revised form 05 December 2011; accepted 14 December 2011

Abstract

In most mammals, prolactin (PRL) is essential for maintaining lactation and its suppression strongly inhibits lactation. However, the involvement of PRL in the control of ruminant lactation is less clear because inconsistent effects on milk yield have been observed with short-term suppression of PRL by bromocriptine. By contrast, in vitro studies have provided evidence that PRL helps to maintain the differentiation state and act as a survival factor for mammary epithelial cells. Therefore, a series of experiments were conducted to assess the galactopoietic role of PRL. In a first experiment, daily injections of the PRL inhibitor quinagolide reduced milking-induced PRL release and induced a faster decline in milk production. Milk production was correlated with PRL released at milking. Quinagolide reduced mammary cell activity, survival, and proliferation. During the last week of treatments, differential milking (1× vs 2×) was applied. The inhibition of milk production by quinagolide was maintained in the udder half that was milked 2× but not in the udder half milked 1×, suggesting that the response to PRL is modulated at the gland level. In a second experiment, cows were injected with quinagolide, quinagolide + injection of bovine PRL at milking time, or water. As in the first experiment, quinagolide reduced milk, protein, and lactose yields. Although PRL injections at milking time were not sufficient to restore milk yield, they tended to increase milk protein and lactose yields and increased the viability of milk-purified mammary epithelial cells. Recently, we investigated the use of quinagolide at drying off. Treating late-lactation cows with quinagolide decreased milk production within the first day of treatment and induced faster increases in somatic cells and bovine serum albumin content in mammary secretions after drying off, which indicates an acceleration of mammary gland involution. In conclusion, these data, combined with data from other studies, provide a good body of evidence indicating that PRL is galactopoietic in dairy cows. However, the response to PRL appears to be modulated at the mammary gland level.

Keywords: Lactation; Mammary gland

1. Introduction

More than 80 yr ago, Stricker and Grueter [1] observed that aqueous pituitary extracts can induce mammary growth and lactation in rabbits. Riddle et al [2] determined that this effect was caused by a hormone

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0739-7240/12/$ – see front matter
doi:10.1016/j.domaniend.2011.12.007

produced by the anterior pituitary, which they named prolactin (PRL). Although PRL mRNA has been detected in the brain and several other tissues (including the mammary gland), the lactotrophs of the anterior pituitary are the predominant source of PRL. Although several hypothalamic substances can act as PRL-releasing factors, secretion of PRL appears to be primarily regulated by the hypothalamus via the inhibitory action of dopamine [3].

Although PRL is one of the first hormones to be identified, its role in ruminant lactation remains controversial. This hormone is mammogenic and lactogenic in both monogastric and ruminant mammals. In most mammals, the suppression of PRL strongly inhibits lactation [4,5]. The short-term administration of bromocriptine—a dopamine agonist that suppresses PRL release—before parturition reduced postpartum milk production in goats [6] and cows [7,8]. However, similar treatments applied during established lactation have produced inconsistent effects on milk yield. In a first experiment, Karg et al [9] injected two cows with increasing doses (20 to 160 mg) of bromocriptine for 3 d and observed an inhibition of PRL without any effect on milk production. However, in a second experiment, Karg et al [9] injected two cows for 7 d (5 d at 150 mg followed by 2 d at 75 mg) and reported a 10% to 20% decline in milk production. Smith et al [10] treated five cows with 80 mg bromocriptine for 2 d but there was no effect on milk production. An early study in goats reported that bromocriptine had no effect on milk yield [11], whereas a subsequent study reported a 21% decrease in milk production after 8 d of treatment [12]. The inconsistent effects of bromocriptine on milk production seen in earlier experiments are probably attributable to short-term administration of the hormone and the small number of experimental animals involved.

The classical way to demonstrate the action of a hormone is to remove its source, observe the changes induced, and try to restore function by hormone replacement. In the 1960s, Cowie and Tindal [13] hypophysectomized lactating goats. In all cases, hypophysectomy caused a sharp decline in milk production that required PRL and other hormones to be restored. In one goat, "goat 34," once milk production had returned to a normal level, the PRL injections were discontinued with no further decrease in milk production [13]. The logical conclusion to draw from that experiment is that PRL is lactogenic but not galactopoietic in goats. However, the situation may not be as straightforward as it seems. Cowie et al [14] reported the results for several other goats. In the seven goats in which the effect of PRL withdrawal was tested, PRL caused a reduction in milk production. Those goats have been forgotten, but goat 34 has not. Goat 34 was given large doses (12.5 mg/d) of growth hormone (GH), and its removal depressed milk production [14]. This GH was pituitary derived and might have been contaminated with PRL, as reported by Skarda et al [15]. In addition, GH and PRL are closely related hormones, and cross-binding activity has been reported when a hormone from one species is used in another species [16]. Skarda et al [15] reported that high-purity bovine GH has weak but significant lactogenic activity in goat mammary tissue that may not be eliminated by PRL antibodies. Accordingly, the bovine GH used for goat 34 may have contained enough PRL-like activity to maintain lactation. Therefore, based on those studies, no conclusion can be reached about whether PRL is galactopoietic in ruminants.

Plaut et al [17] injected eight cows with a daily dose of 120 mg PRL for 14 d without affecting milk production. Although the injections increased basal plasma PRL two- to fivefold, they reduced the milking-induced release of PRL considerably. Conversely, the injection of a much smaller dose of PRL (1 μg/kg body weight [BW]) twice a day for the first 3 wk of lactation increased milk production [18]. In goats, recombinant PRL injections increased milk yield by over 10%, an increase that was comparable and additive to that elicited by GH [19]. Further evidence of the galactopoietic action of PRL relates to the fact that a long-day photoperiod increases the PRL concentration and milk production [20,21], whereas the administration of melatonin, a neurotransmitter produced during the night, for 12 wk decreased PRL and milk production [22]. Again, based on these studies no conclusion can be made about whether PRL is galactopoietic in ruminants.

In contrast with the inconsistent galactopoietic effect of PRL observed during in vivo experiments, PRL clearly modulates the differentiation state and the survival of ruminant mammary epithelial cells in vitro. PRL stimulates the synthesis of milk constituents such as casein and lipids in ruminant mammary explants or cultivated mammary epithelial cells [23–25]. In addition to having an effect on cell differentiation, PRL also stimulates the proliferation of bovine mammary epithelial cells [26]. This effect is probably caused by the ability of PRL to increase activating protein-1 transcriptional complex activity via c-Jun amino terminal kinase activation. Moreover, PRL protects bovine mammary epithelial cells from apoptosis by suppress-