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Review

Prolactin in the Male: 25 Years Later

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In an article published 25 years ago in the first volume of the *Journal of Andrology* (Bartke et al, 1980), we reported evidence of involvement of prolactin (PRL) in the control of testicular growth in the golden hamster. In this seasonally breeding species, testes undergo regression in the fall and recover their size and activity the following spring. PRL-secreting transplants of anterior pituitaries augmented the stimulatory effect of treatment with human chorionic gonadotropin on the recrudescence of the regressed testes, while treatment with an inhibitor of PRL release, bromocriptine, delayed recrudescence of the testes and the seminal vesicles induced by exposure to long photoperiods.

Role of PRL in the Control of Seasonal Breeding in the Male Hamster

Studies conducted in our laboratory following the above-referenced report of the effects of bromocriptine (Bartke et al, 1980) reaffirmed the role of photoperiod-induced alterations in plasma PRL levels in the control of seasonal transitions between periods of full testicular activity and testicular quiescence in the golden hamster and identified a number of mechanisms involved in the actions of PRL. In the male golden hamster, PRL acts at multiple levels of the hypothalamic-pituitary-testicular axis. In the hypothalamus, it modifies the turnover of neurotransmitters involved in the control of the pituitary (Steger et al, 1982, 1984, 1986). In the pituitary, it influences the number of androgen receptors (Prins et al, 1988). Actions of PRL on the hypothalamic-adenohypophyseal system result in the stimulation of follicle-stimulating hormone (FSH) synthesis and release (Bartke et al, 1981; Steger et al, 1983; Carrillo et al, 1984) and reduction of the sensitivity of gonadotropin release to negative testosterone feedback (Bartke et al, 1984; Matt et al, 1984). This latter effect is of particular interest, because the major shifts observed in the sensitivity of luteinizing hormone (LH) and FSH release to feedback control by gonadal steroids accompany annual cycles of reproductive activity in both sexes of many (presumably all) seasonal breeders and are critically important for transitions between reproductive activity and quiescence. Reduced sensitivity of the hypothalamus and the pituitary to negative feedback of sex steroids during annual reactivation of the gonads resembles the endocrine changes that take place during

puberty in both seasonal and nonseasonal breeders, including humans.

In the hamster testis, PRL, along with the gonadotropins, regulates the expression of its own receptors (Klemcke et al, 1984, 1986; Amador et al, 1985) and LH receptors (Bex et al, 1978; Klemcke et al, 1981) and enhances the responsiveness of Leydig cells to LH stimulation (Klemcke et al, 1986).

The net result of the actions of PRL can be very striking. Golden hamsters with regression of the testes that was induced by 2 months of exposure to short photoperiods are found to respond to 2 months of treatment with PRL-secreting ectopic pituitary transplants by the restoration of their fertility (Bartke et al, 1979). Our earlier studies of hypophysectomized rats (Hafiez et al, 1972) and mice (Bartke, 1971) and of hypopituitary dwarf mice (Bartke, 1966; Bartke and Lloyd, 1970) demonstrated the similar, although generally far less dramatic, stimulatory effects that PRL has on testicular activity. These studies also suggested that increases in the number of LH receptors and in the sensitivity of testicular steroidogenesis to LH stimulation are important in mediating the effects of PRL on male reproductive function in these species of rodents.

The obvious and important question raised by these findings was whether the results obtained in hamsters, mice, and rats also apply to other mammalian species. It was also not entirely clear how to relate the results of our research probing the physiological role of PRL in the male to the rapidly accumulating evidence that pathologically elevated levels of PRL, hyperprolactinemia (hyperPRL), can interfere with testicular function, libido, potency, and fertility. This article will briefly review the highlights of studies that have addressed the role of PRL in different species of seasonally breeding mammals and studies that have used targeted silencing or overexpression of PRL or PRL receptor (PRL-R) genes to identify the physiological role of PRL in the control of male reproductive functions. The concluding section will address differences between the responses to normal and abnormally elevated levels of PRL and differences between the role of PRL in males of different species.

Role of PRL in the Control of the Annual Reproductive Cycles in the Black Bear and the Polar Bear

A series of elegant studies in Dr Bahr's laboratory used captive and free-ranging bears to determine whether the role of PRL in the control of male reproductive seasonality applies to species taxonomically distant from rodents. In the black bear (*Ursus americanus*), serum PRL levels were minimal in December, when animals were in the den, and increased beginning in March, reaching maximal values in May (Tsubota et al, 1995). Thus, seasonal increases in serum PRL levels coincided with testicular recrudescence and the onset of breeding season and preceded peak testosterone concentrations, which were achieved in June (Tsubota et al, 1995). The expression of testicular gonadotropin and PRL-R genes was examined before and during the breeding season (in January and May, respectively) (Howell-Skalla et al, 2000a). The major PRL-R transcript was present in both January and May, whereas minor transcripts were detected only in May, coinciding with the increased abundance of LH receptor (LH-R) messenger RNA (mRNA). A subsequent study demonstrated an increase in the abundance of LH-R and PRL-R mRNA between January and March (Howell-Skalla et al, 2000b). Suppression of serum PRL levels during testicular recrudescence by treatment with a long-acting dopaminergic agonist prevented an increase in the expression of LH-R and PRL-R in March, lowered serum testosterone levels in March and April, and reduced testis size in May (Howell-Skalla et al, 2000b). These findings strongly imply that increased release of PRL before the onset of the breeding season plays a physiological role in the ensuing stimulation of testicular function in the black bear. Moreover, the mechanisms involved in this effect of PRL appear to resemble those described in the hamster and in nonseasonally breeding rodents.

In the follow-up of these studies, plasma hormone levels and testicular size were examined in free-ranging polar bears (*Ursus maritimus*) during the mating season in April and May and after the mating season in July and October (Howell-Skalla et al, 2002). Plasma LH and testosterone levels were maximal in April, highest levels of PRL were measured in April and May, and testes reached maximal size in May. Thus, seasonal elevation of PRL levels in polar bears coincides with the breeding season, but further studies are required to determine whether PRL plays a role in stimulating a seasonal increase in testicular activity in this species.

Does PRL Have a Role in Short-Day Breeders?

The release of PRL depends on the photoperiod, with long days being stimulatory and short days inhibitory. This raises the possibility that in short-day (fall) breeders, such as sheep or deer, PRL either has no role in the control of reproduction or is involved in the seasonal inhibition rather than the seasonal stimulation of testicular growth and activity. Several laboratories probed the suspected involvement of PRL in mediating the effects of photoperiod on testicular function in the ram. Most of these studies involved treatment with bromocriptine, an inhibitor of PRL release, during different phases of the annual cycle of reproductive activity. Although the effects of bromocriptine were generally small and not always consistent between the studies, they did include reductions in testis size, sperm production, and testosterone secretion (Sanford and Dickson, 1980; Barenton et al, 1982; Yarney and Sanford, 1989; Regisford and Katz, 1993) and a delay in the response of the testes to a short (stimulatory) photoperiod (Barenton and Pelletier, 1980; Sanford and Dickson, 1980). Differences between the results of the various studies are probably related to differences in the breed of the animals and in the experimental protocols. The possibility that PRL exerts direct, rather than gonadotropin-mediated, effects in the ovine testes is strongly supported by the presence of PRL-Rs in the Leydig cells and the seminiferous tubules of this species (Lincoln et al, 2001) and by results obtained in rams with surgical disconnection of the pituitary from the hypothalamus (Lincoln et al, 1996). This procedure suppresses gonadotropin release and disrupts the inhibitory control of PRL release by tuberoinfundibular dopaminergic neurons. In such animals, alterations in PRL release induced by photoperiod or bromocriptine are followed, within 4–8 weeks, by corresponding changes in the size of the testes (Lincoln et al, 1996; Lincoln and Clarke, 1997).

Collectively, the results obtained in different breeds of sheep suggest that PRL contributes to the control of seasonal alterations in testicular function in short-day breeders, although the magnitude of its effects is much smaller than in some rodents and carnivores that breed in the spring.

Physiological Role of PRL in the Male Revisited; PRL-R Knockout and PRL Knockout Mice

The availability of mice with targeted disruption (knockout [KO]) of the gene responsible for the production of PRL or PRL-R (Horseman et al, 1997; Ormandy et al, 1997) provided an exciting opportunity to reexamine the physiological functions of PRL signaling, including its role in the control of male reproduction. The absence of functional PRL-Rs in PRL-R-KO mice was originally reported to be associated with infertility or reduced fertility in approximately half of the males (Ormandy et al, 1997). However, subsequent studies of male reproductive functions in these animals produced conflicting results. Binart et al (2003) reported no alterations in the weight of the testes, epididymides, and sex accessory glands, in the plasma levels of gonadotropins and testosterone, or in the fertility of PRL-R-KO males and concluded that "the absence of PRL signaling is not detrimental to male testicular function and to fertility in the mouse." However, in a paper published during the same year, Robertson et al (2003) reported an increased rate in the total infertility of PRL-R-KO mice, along with an increased latency to produce a first pregnancy.

Isolated PRL deficiency in PRL-KO mice was associated with reductions in the weight of the seminal

vesicles and the ventral prostate, in the levels of plasma LH, and in the pituitary release of LH and FSH in vitro (Steger et al, 1998). However, plasma testosterone levels, in vitro testosterone release, and fertility were not affected. It is unclear why the lack of PRL signaling in PRL-R-KO and PRL-KO mice affects the reproductive function of the male mouse in such a way that the expected results are marginal compared with those obtained in hypophysectomized or PRL-deficient hereditary dwarf mice or even absent. Perhaps normal or near-normal reproductive function in PRL-R-KO and PRL-KO animals is due to compensatory mechanisms and/or alternate signaling pathways (eg, growth hormone [GH]) that are absent in both hypophysectomized animals and hereditary dwarf mice. Such a possibility is consistent with the observation that plasma PRL levels are increased in GH-R-KO mice (Chandrashekar et al, 1999). That the male reproductive functions appear to be more vulnerable to deletions of the gene responsible for producing PRL-R than to deletion of the gene responsible for producing PRL could be due to developmental effects in PRL-R-KO animals, which are presumably unable to respond to placental lactogens or maternal PRL, including the PRL present in the milk.

Recent Progress in Understanding the Action of PRL on the Prostate

The action of PRL on the male accessory reproductive glands, including the prostate, has been extensively studied for more than 50 years, and a comprehensive review of the advances in this field during the past 25 years is outside the scope of this brief article. However, we note how much progress was made possible by the development of methods for gene knockout and for production of transgenic animals, especially when it became possible to target gene expression to specific organs.

A report on the reduced weight of the ventral prostate and seminal vesicles in PRL-KO mice without changes in plasma testosterone levels (Steger et al, 1998) indicates that PRL has a physiological role in the structural maintenance of these organs and that it acts directly on the male accessory reproductive glands. Unexpectedly, the weight of seminal vesicles and prostate was not altered in PRL-R-KO mice (Binart et al, 2003). However, the number of epithelial cells in the dorsal prostate was diminished in these animals, and simian virus 40 T-induced neoplasia was reduced in the ventral lobe (Robertson et al, 2003).

A massive enlargement of accessory reproductive glands was described in old transgenic mice that overexpressed human GH or human placental GH variant hormones, which signal via both GH receptors and PRL-Rs in the mouse (Prins et al, 1992). These findings reaffirm the stimulatory actions of PRL on the male reproductive system, because the overexpression of bovine GH, which is not lactogenic in the mouse, failed to produce similar changes (Prins et al, 1992). In more recent studies, transgenic mice with a ubiquitous overexpression of PRL that was driven by a metallothionein-1 promoter had elevated serum androgen levels and a dramatic enlargement of the prostate (Wennbo et al, 1997). Prostate-specific expression of rat PRL that was under the control of rat probasin (Pb) promoter led to stromal hyperplasia, ductal dilatation, focal epithelial dysplasia, and an increased stromal-to-epithelial ratio without changes in serum androgen levels (Kindblom et al, 2003). Microarray analysis of hyperplastic prostates from Pb-PRL transgenic mice showed altered expression of more than 250 genes and provided evidence for reduced apoptosis, increased tissue remodeling, and activation of the stroma (Dillner et al, 2003). These changes, together with the evidence for local expression of PRL in the prostate (Nevalainen et al, 1997; Härkönen, 2003), raise many new and important questions about the potential role of PRL in prostatic hyperplasia and cancer in men.

New Information on the Role of PRL in Men

A discussion of the progress in the understanding of the role of PRL in male reproductive functions would not be complete without reference to findings in the human. Research results reported during the past 25 years have added to the evidence that pathological hypersecretion of PRL (hyperPRL) in

men is associated with hypogonadism and/or impotence and that the effects of PRL on the central nervous system control of gonadotropin release and sexual behavior are important in the etiology of these disorders (see reviews in Bartke and Shrenker, 1987; DeRosa et al, 2003).

Identifying the physiological role that PRL has on male sexual function, endocrine regulation, and fertility in our own species continues to be an interesting challenge. Indirect support for the involvement of PRL in controlling the steroidogenic and gametogenic functions of the human testis and influencing the male reproductive tract was provided by studies of PRL binding. Hair et al (2002) reported localization of PRL-Rs in human Leydig cells, spermatocytes, and spermatids and in the epithelium of the epididymis, vas deferens, prostate, and seminal vesicles. Studies of various steps of PRL signaling in fresh samples of vas deferens have suggested the functional activation of PRL-Rs in this tissue (Hair et al, 2002). Other investigators have described the beneficial effects of PRL and metoclopromide (a PRL releaser) on sperm characteristics in infertile men (Ufearo and Orisakwe, 1995), and in men with prostatic cancer, investigators have described the potentiation of antigonadal effects of a gonadotropin-releasing hormone agonist by bromocriptine, an inhibitor of PRL release (Huhtaniemi et al, 1991).

Krüger et al (2003a) reported that plasma PRL levels in men increase immediately after orgasm. The same investigators examined the consequences of pharmacological manipulation of PRL release on arousal, orgasm, and refractory period (Krüger et al, 2003b). Suppression of PRL secretion with cabergoline enhanced all of the examined parameters of sexual drive and function. Stimulation of PRL release with protirelin had no significant effects on these parameters but completely prevented the effects of cabergoline. The authors suggested that post-orgasmic PRL release has a function in inhibiting sexual drive and behavior (Krüger et al, 2003b).

Effects of PRL in Hamsters vs Current View of the Role of PRL in the Male

By studying the effects that treatment with bromocriptine, PRL, or PRL-secreting ectopic pituitary transplants has on male golden hamsters, we have obtained evidence that PRL is involved in the control of seasonal breeding in this species. What can be said about the significance of these findings from the perspective of 25 years? First, these findings firmly establish that PRL can have a major role in mediating the effects of photoperiod on male reproductive functions and that PRL can facilitate the identification of the mechanisms involved in these effects. Work in other laboratories indicates that the conclusions concerning the role of PRL in the seasonal breeding of male golden hamsters apply to other, but clearly not all (DiGregorio et al, 1994), seasonal breeders. The strongest evidence for the importance of PRL in the control of the annual cycle of testicular activity in a species other than golden hamsters was obtained in studies of black bears (Howell-Skalla et al, 2000b). It is interesting that photoinducible changes in PRL release in Japanese quail are associated with corresponding changes in testicular growth (Yasuo et al, 2004). From the evidence available to date, it appears that golden hamsters are not unique in using PRL for the purpose of mediating the effects of photoperiod on the testis but that the magnitude of these effects of PRL on male gonadal function in this species may be exceptional. In the gonadally regressed hamsters, PRL acts on the hypothalamus and pituitary to stimulate gonadotropin release, and a combination of this effect with the direct effects of PRL on the testis leads to dramatic stimulation of testicular growth and function. gonadally active adult male hamsters, experimentally creasing plasma PRL to levels above the physiological range produced significant increases in plasma FSH testosterone levels, testicular weight, and release of and testosterone in vitro (Bartke et al, 1982). Stimulation of gonadotropin release by hyperPRL is not unique to golden hamster, since it also occurs in the nonseasonally breeding mouse (Klemcke and Bartke, 1981), but it stands in sharp contrast to the inhibitory action of hyperPRL gonadotropin release in the rat and the human (for

views, see Bartke and Shrenker, 1987; De Rosa et 2003).

It is unclear whether, and to what extent, the dramatic differences observed between species in their responses to hyperPRL coincide with differences in the physiological role of PRL in the regulation of the testis. Stimulatory, potentiating, and synergistic effects of PRL on ious aspects of testicular growth and function were demonstrated in hamsters and mice in which hyperPRL stimulatory, as well as in rats, in which it is inhibitory (for a review, see Bartke et al, 1985). Similar to the uation in the rat, both hypo- and hyperprolactinemia detrimental to testicular function in the domestic (Jedlinska et al, 1995).

In the human, there is mounting evidence that normally acts on the Leydig cells, germ cells, prostate, vas deferens, and other regions of the male reproductive tract, but the role of these actions in the normal remains to be clearly defined.

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Footnotes

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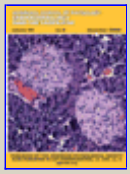

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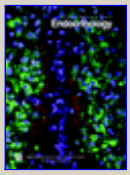

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