MINIREVIEW

Seasonal Changes in the Function of the Hypothalamic-Pituitary-Testicular Axis in the Syrian Hamster (43340A)

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In the overwhelming majority of animal species, reproductive functions exhibit pronounced annual rhythmicity. Fertility is usually restricted to a particular and often a very brief period of the year, the breeding season. The Syrian (golden) hamster, *Mesocricetus auratus*, is a very popular model for the study of seasonal breeding, and a substantial part of what is known about the mechanisms of environmental control of mammalian reproduction is derived from experiments conducted in this species.

Golden hamsters have a relatively restricted geographic range and commercially available laboratory stocks are derived from a few animals collected over 50 years ago in northern Syria (1). In their natural habitat, hamsters breed in the spring and fall and hibernate during the winter. Under laboratory conditions, they remain reproductively active throughout the year, as long as they are exposed to long photoperiods, i.e., at least 12.5 hr of light per day. However, the transfer of adult animals to a short photoperiod (i.e., less than 12 hr/day) or complete darkness at any time of the year triggers a sequence of changes in their neuroendocrine and reproductive functions that appears to mimic the processes that normally occur during the fall, winter, and early spring. These changes include (i) repression of the testes, (ii) a period of gonadal atrophy and functional quiescence, and (iii) spontaneous recovery ("recrudescence") of testicular size and activity. The amplitude of these changes is enormous, with reduction of testicular weight by at least 80%, comparable decreases in the size of other parts of the male reproductive system, complete cessation of spermatogenesis, substantial reduction in the blood levels of the male sex hormone, testosterone, and loss of libido (2, 3). These responses to a short photoperiod can be prevented by surgical removal of the pineal gland and mimicked by properly timed melatonin injections and thus are obviously mediated by photoperiod-related changes in the secretory function of the pineal (2). There is a substantial amount of evidence that photoperiod indeed influences the pineal, that the pineal product melatonin alters hypothalamic control of synthesis and secretion of several hormones by the anterior pituitary gland, and that reduced release of these hormones is, in turn, responsible for testicular atrophy. Although these responses of male golden hamsters to photoperiods providing less than 12.5 hr of light per day are extremely consistent, their exact timing and, to a lesser extent, their magnitude depend also on ambient temperature (4), previous photoperiod history (5), strain (6), and the social environment (7) of the animals.

Changes in the pituitary and testicular function opposite to those described above take place some 3 ½–4 ½ months after the transfer to inhibitory photoperiods. They are apparently driven by an endogenous "biological clock" and lead to complete recovery of testicular function and fertility (2, 3). It is the purpose of this brief review to discuss pineal, hypothalamic, pituitary, and testicular mechanisms that are believed to be involved in the seasonal transitions between the states of gonadal activity and quiescence in the male Syrian hamster.

Neuroendocrine Changes Associated with Testicular Regression and Recrudescence

Despite the abundance of data on the endocrine consequences of altered photoperiods, we are just be-

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ginning to understand some of the neuroendocrine mechanisms responsible for photoperiod-induced changes in pituitary function. In other species, such as the rat, a number of recognized and putative hypothalamic neurotransmitters and neuromodulatory substances have been shown to mediate hypothalamic hypophysiotropic hormone release, which in turn regulates pituitary hormone synthesis and release (8–10). It is likely that these same agents mediate the effects of photoperiod on the hamster reproductive axis.

Pineal

Melatonin Rhythms/Levels. The pineal gland is essential for the photoperiodic control of the hamster's reproductive function (2). Pinealectomized hamsters show normal reproductive function under long photoperiods, but do not respond to short photoperiods. Afternoon, but not morning, melatonin injections can mimic the effects of short photoperiods in intact or pinealectomized Syrian hamsters (11).

Melatonin levels in the pineal and, presumably, the circulation show a very distinct rhythm, with marked elevations during the dark phase of the photoperiod or at regular intervals in animals housed under constant dark conditions (2, 12). It is assumed that this melatonin rhythm conveys a time signal, but the nature of the signal indicating change in day length has been the subject of considerable debate. However, the majority of evidence now suggests that it is the duration of the nighttime melatonin rise that signals day length (13). The golden hamster responds to a lengthening melatonin signal with gonadal regression, whereas the opposite is seen in short-day breeders such as the sheep.

Melatonin Receptors. Although it has been known for some time that melatonin modulates the circadian and seasonal timing of a number of physiological processes, including most notably reproduction, possible sites of action where melatonin might mediate these effects are just now being identified. Some earlier reports indicated the presence of [^{3}H]melatonin binding sites in the bovine hypothalamus and hamster brain (reviewed in Ref. 14), but characteristics of specific melatonin receptors have been only recently described when the high affinity, high specific activity ligands became available (15–18).

Binding sites for 2-[^{125}I]iodomelatonin (^{125}I-melatonin) exhibit a marked difference in distribution and pharmacological characteristics between species and within a species, as reported by different laboratories (18, 19). There are also discrepancies between conclusions made from autoradiography data and those from studies using tissue homogenates due to the existence of high and low affinity binding sites. It has been proposed that two distinct melatonin receptors might exist, a high affinity receptor, such as seen in the chicken retina and brain or the rat pars tuberalis, and a lower affinity binding site, such as those found in the hamster brain (19, 20). However, the existence of two classes of binding sites has been debated and additional data are needed to resolve differences in results from different laboratories (18, 21).

Studies using tissue homogenates show ^{125}I-melatonin binding sites in the cerebral cortex, cerebellum, hypothalamus, brainstem, olfactory bulb, striatum, and pituitary, with binding sites being most abundant in the hypothalamus and brainstem (20, 21). Autoradiographic studies have reported ^{125}I-melatonin binding sites in the suprachiasmatic nuclei, median eminence, paraventricular nuclei, pituitary, and pineal (22–24). However, it has also been reported that ^{125}I-melatonin binding can be found only in the median eminence and pituitary, but not in other brain areas subjected to autoradiographic analysis (25). Melatonin binding is consistently found in the pars tuberalis, and many of the reports of the presence or absence of melatonin binding in the pituitary or median eminence depend on the method of separation of these tissues at autopsy. Melatonin binding sites in the hamster, at least in the anterior paraventricular nucleus, are neuronal, since neurotoxins injected into the anterior hypothalamic area prevent ^{125}I-melatonin binding (24). The role of the pars tuberalis in controlling pituitary function is not understood, but its location between the median eminence and anterior pituitary may suggest a locus of control. The ventral medial nucleus and preoptic area are also possible sites of melatonin action, based on binding and implant data.

Diurnal changes in [^{3}H]melatonin binding in the rat and hamster brain were reported a number of years ago (26), but newer data in the rat using ^{125}I-melatonin are inconsistent (27–29). Similar data in the hamster have not been published to our knowledge.

The presence of melatonin receptors or binding sites in the suprachiasmatic nucleus (SCN), the ability of melatonin to modulate metabolic activity of the SCN, and the ability of melatonin injections to reset various biological rhythms strongly support the importance of the pineal and the SCN in the control of circadian rhythmicity (30). In the white-footed mouse, medial preoptic-suprachiasmatic melatonin implants induce gonadal regression, suggesting that this is an important site of melatonin action in controlling reproductive function (31). In the Syrian hamster, intrahypothalamic melatonin implants can block photoperiod responsiveness (32). Although reproductive activity is regulated by a circadian clock, the SCN may not have a direct role in mediating the effects of melatonin on testicular regression, since SCN lesions alter, but do not block, the ability of properly timed melatonin injections to induce gonadal regression in the golden hamster (33).

Hypothalamus

Pituitary Luteinizing Hormone-Releasing Hormone Response. It appears that short photoperiod (short day [SD])-induced changes in gonadotropin levels are secondary to changes in hypothalamic function, since *in vivo* and *in vitro* studies strongly support the hypothesis that the pituitary's response to luteinizing hormone-releasing hormone (LHRH) is not an important factor causing short photoperiod-induced reductions of serum luteinizing hormone (LH) or follicle-stimulating hormone (FSH). Thus, male hamsters maintained for 10 weeks in a short photoperiod responded to subcutaneous injections of from 2 ng to 200 ng LHRH similarly to hamsters maintained in long days (34). A similar lack of photoperiod effects on LHRH response was also seen in a study in which influences of testosterone on LH and FSH secretion were eliminated by castration (35). Finally, a number of studies have demonstrated that hemipituitaries or dispersed cell cultures from gonadally regressed hamsters can still release LH in response to LHRH (36–39). The *in vitro* FSH response to LHRH has been reported to be unchanged or even enhanced after SD exposure (37–39).

LHRH Content and Release. As discussed above, most evidence suggests that photoperiod-induced testicular regression is not due to an inability of the pituitary to respond to LHRH. These findings provided the impetus for several investigations concerning the possible effects of photoperiod on the regulation of synthesis and release of LHRH in the hypothalamus. Several laboratories using radioimmunoassay procedures reported that hypothalamic LHRH content either increases slightly or is not changed during testicular regression (34, 40, 41) and offered a speculative conclusion that SD causes a decrease in LHRH release without a concomitant change in LHRH synthesis. Support for the hypothesis that short days inhibited LHRH release without inhibiting the ability of the neuron to synthesize LHRH was provided by immunohistochemical studies in which it was demonstrated that perikarya of LHRH neurons are significantly larger in gonadally regressed than in nonregressed hamsters and that there are no photoperiod-related differences in the number or the proportion of monopolar versus bipolar LHRH neurons (42).

Techniques providing a more direct estimate of LHRH release have been established, but the data are often contradictory and difficult to interpret. A study (published only in abstract form) using push-pull perfusion of the hypothalamus suggested that LHRH release is enhanced by SD exposure (43), but the results have not been confirmed, to the best of our knowledge. We have demonstrated recently that LHRH release *in vitro* was significantly greater from whole hypothalami of long day (LD) as compared to those of SD hamsters, although there was no difference in the percentage of increase of LHRH release after stimulation with 10^{-7} *M* norepinephrine (R. W. Steger, unpublished data). These studies still need to be confirmed and additional studies need to be undertaken to establish whether differences in LHRH release are due to changes in the LHRH-secreting neurons themselves or to the function of other types of neurons in the hypothalamus that may either inhibit or stimulate LHRH release.

Hypothalamic Biogenic Amines. In other species, a number of established and putative neurotransmitters have been shown to have a role in controlling pituitary hormone synthesis and release by controlling the release of hypothalamic hypophysiotropic hormone secretion. Although we are a long way from understanding all of the control mechanisms for gonadotropin release, many investigators agree that norepinephrine (NE) is the principal neurotransmitter stimulating LH and FSH release (8, 9). The role of dopamine (DA) in controlling LH and FSH release is still not completely understood, but it is clear that DA is among the most important factors controlling prolactin (PRL) release.

It seemed likely that NE and DA could be involved in seasonal changes in reproductive function, and some years ago, we established that SD-induced testicular regression is accompanied by, and most likely the partial results of, changes in hypothalamic catecholamine metabolism (40). In these studies, it was demonstrated that male hamsters transferred from a long (14:10-hr light-dark) to a short (5:19-hr light:dark) photoperiod for 10 weeks had a significantly lower rate of hypothalamic NE turnover, an estimate of NE neuronal activity, than did control animals maintained in a long photoperiod. Furthermore, it was also demonstrated that hypothalamic NE turnover rates returned to LD control levels several weeks prior to the time that testicular recrudescence was observed. If hamsters were pinealectomized prior to SD exposure, they not only failed to show a decrease in LH, FSH, PRL, and testicular weight, but the SD-induced decrease in median eminence NE turnover was also blocked (44). Subsequent studies from Benson's (45) and from our laboratories (46) established a temporal relationship between decreasing plasma LH levels and reductions in median eminence and medial basal hypothalamic NE turnover (Fig. 1). Additional support for a primary role of NE in the control of seasonal reproductive activity was provided by experiments in which it was demonstrated that NE turnover and plasma LH levels could be stimulated in regressed male hamsters by L-dopa or L-DOPS administration and that the rise in LH and FSH associated with LD-induced testicular recrudescence could be inhibited by the blockade of NE synthesis with α-methyl-*p*-tyrosine (44; R. W. Steger, unpublished results).

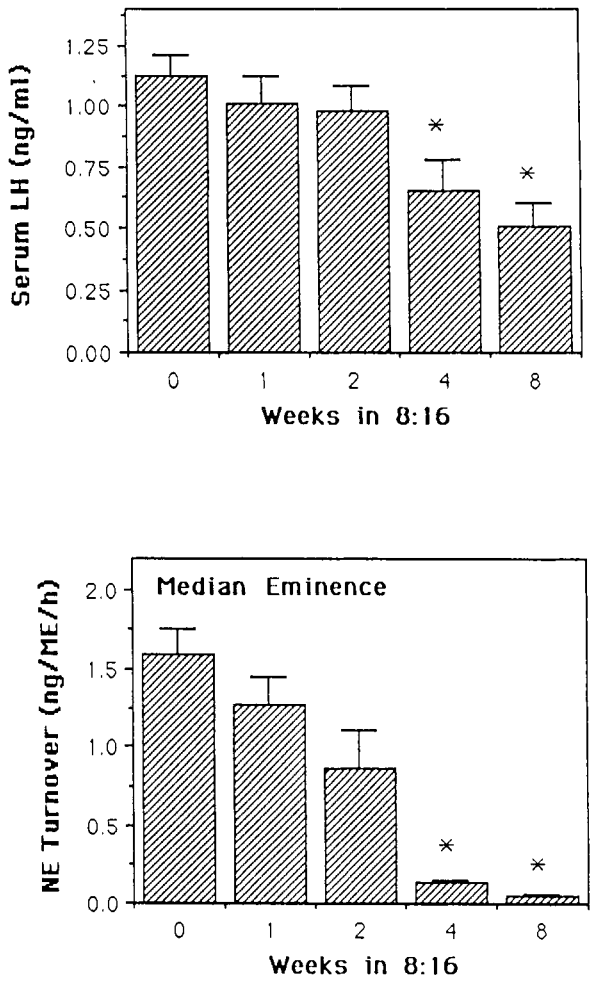

Figure 1. The effects of time in a short photoperiod (8:16-hr light:dark) on serum LH levels and median eminence norepinephrine turnover. The values are expressed as mean ± SE and the asterisk denotes statistical significance ($P < 0.05$) versus the long photoperiod controls (0 weeks in 8:16-hr light:dark). Turnover was calculated from the rate of norepinephrine depletion following the inhibition of tyrosine hydroxylase with a-methyl-*p*-tyrosine and provides an estimate of neuronal activity. (See Ref. 46 for details.)

Exposure to short days also causes marked changes in DA turnover in several hypothalamic regions. In the median eminence region, DA turnover is significantly decreased within 1 week of SD exposure and remains low throughout the period of testicular regression, whereas in the medial basal hypothalamus, DA turnover initially rises and then returns to levels comparable to those in LD controls (Fig. 1) (45, 46). Spontaneous or LD-induced testicular recrudescence stimulates hypothalamic DA turnover (40, 44) and pinealectomy blocks the effects of photoperiod on DA (47). Despite the marked effects of photoperiod on DA metabolism, the physiologic relevance of these changes is still unclear. Prolactin administration reverses the effects of SD on median eminence DA turnover, suggesting that the decrease in DA turnover in this region is secondary to a lack of negative feedback on the tuberoinfundibular dopaminergic system by endogenous PRL (48; R. W. Steger and E. Gay-Primel, unpublished data). However, SD-induced changes in median eminence DA turnover clearly precede the decrease in PRL levels (46), making it unlikely that reduced DA turnover is only the result of decreased PRL levels. The reduction in DA turnover might be expected to lead to increased pituitary PRL secretion, but the pituitaries of regressed hamsters show increased inhibitory responses to DA (38, 48).

Hypothalamic serotonin (5-HT) turnover is significantly increased in the medial basal hypothalamus of the SD as compared with the LD hamster, whereas 5-HT turnover in the median eminence and anterior pituitary remains unchanged (49). The temporal responses of 5-HT metabolism to SD exposure have not been reported, but 5-HT turnover in fully regressed hamsters is returned to control (LD) levels within 2 days of LD exposure (49). Since these changes precede increases in plasma LH levels and since 5-HT is often inhibitory to LH release in many species, including the hamster (8, 9; R. W. Steger, unpublished observations), it is possible that 5-HT may have an important role in photoperiod-induced changes in LH secretion. Hypothalamic 5-HT content shows very distinct day-night differences, but these diurnal variations appear to be unaffected by changes in day length (50).

Role of Excitatory Amino Acids. Considerable evidence has established a role for excitatory amino acids such as *N*-methyl-D-aspartate in the control of LH and FSH release in the rat (51–53) and it is likely that similar relationships may hold for the hamster. Daily *N*-methyl-D-aspartate injections blocked the effects of short days on testicular regression and induced testicular recrudescence in SD hamsters with fully regressed testes (54). Normally, periodic light pulses (once a week) given 6 hr after lights off can prevent SD-induced testicular regression. However, if hamsters are treated with MK-801, a specific antagonist of the *N*-methyl-D-aspartate subclass of excitatory amino acid receptors, testicular regression still occurs in the presence of this normally stimulatory light pulse (55). Since MK-801 also blocks the inhibitory effects of light pulses on pineal melatonin release, it appears that excitatory amino acids may mediate the effects of light on the reproductive axis by modulating melatonin secretion. An earlier study, which demonstrated that MK-801 blocked the effects of light on pineal melatonin content, but did not directly change pineal melatonin content, suggests that MK-801 might be working in the SCN or between the retina and the SCN (56).

Opiate Peptides. There is increasing evidence that the endogenous opioid peptides have an important inhibitory role in controlling pituitary gonadotropin release and that these effects of opiates are markedly affected by gonadal steroids (8, 9). Injections of an

opiate receptor antagonist, naloxone, can delay, but not prevent, SD-induced testicular regression, presumably by stimulating pituitary LH secretion (57), but they fail to induce gonadal recrudescence or LH release in fully regressed male hamsters with or without testosterone replacement (58, 59).

Wilkinson and his co-workers (60) demonstrated that the uptake of [^{3}H]naloxone in the hypothalamus is not affected by short photoperiod exposure, but whole brain naloxone binding is slightly increased. More detailed studies demonstrate that short-day exposure caused a decrease in [^{3}H]naloxone binding to the medial amygdala and the intercalated amygdaloid nucleus, but did not affect opioid binding in the hypothalamus or preoptic areas of the male hamster brain (61). These changes were blocked by superior cervical ganglionectomy, which renders the pineal nonfunctional. In the same study, lesions of the medial amygdala did not affect gonadal regression. Testosterone negative feedback in long days was enhanced by the medial amygdaloid lesions, but the lesions did not affect feedback in short-day hamsters.

Other Neurotransmitters Possibly Involved in Photoperiod Responses. A role for acetylcholine (ACH) in the control of pituitary hormone secretion in the hamster has not been studied, but in the male rat, ACH appears to be stimulatory to LH release and perhaps also inhibitory to PRL release (9, 10). Possibly of more significance is the role that ACH may play in the control of circadian rhythms or in the recognition of day length. The suprachiasmatic nucleus, the presumed site of a (or the) biological clock, is richly innervated with cholinergic fibers, and ACH administration changes the firing rate of SCN neurons (62). Furthermore, in the hamster, properly timed intracerebroventricular injections of the ACH agonist, carbachol, can prevent the inhibitory effects of short photoperiod on reproductive function, presumably by disrupting the timekeeping function of the SCN or other circadian oscillators (63).

Pituitary

Exposure to a short photoperiod leads to the suppression of FSH and, subsequently, PRL and LH release with the profound reduction in the incidence of LH secretory episodes ("pulses") (2, 3, 14, 64, 65). The reported instances of short photoperiod-induced testicular regression with little or no reduction in plasma gonadotropin levels (66) remain unexplained and could conceivably represent either a secondary increase due to diminishing inhibitory signals from the regressed gonads or artifacts of analyzing pulsatile phenomena on the basis of single, rather than sequential, measurements. The photoperiod-related reduction in gonadotropin release is presumably due to reduced noradrenergic input to LHRH-secreting neurons, which was discussed in the preceding section. Several lines of evidence support a causal relationship between norepinephrine turnover in the medial basal hypothalamus/median eminence and plasma LH and FSH levels (8–10, 44). Seasonal suppression of gonadotropin release is strongly associated with and perhaps due to a concomitant increase in the sensitivity of the mechanisms controlling gonadotropin release to gonadal steroid feedback (67–69). Although the relative importance of this phenomena and the steroid-dependent versus steroid-independent mechanisms in the seasonal suppression of LH and FSH is subject to much debate (70), there is no doubt that this very major shift in the responsiveness to inhibitory testicular signals is of considerable physiologic importance. It overrides the expected negative feedback control of the pituitary and allows simultaneous reduction in plasma levels of gonadotropins and testosterone.

In an attempt to identify the mechanism(s) responsible for the photoperiod-related changes in the responsiveness of gonadotropin release to androgen feedback, several laboratories examined concomitant changes in pituitary androgen binding. Results available to date include evidence for reduced nuclear and increased cytosolic androgen binding in the pituitaries of SD-exposed hamsters (71–74). These observations could be taken as evidence either for or against the involvement of changes in pituitary androgen receptors in seasonal changes in sensitivity to testosterone feedback. Their interpretation is further complicated by the recent debate about the relationship of cytosolic receptors to the localization of steroid binding sites in living cells. However, some support for the suspected physiologic role of alterations in the number of pituitary androgen receptors in seasonal breeders was provided by the recent study by Prins *et al.* (74), who reported that in castrated hamsters in which plasma testosterone levels were held constant by means of a subcutaneous, testosterone-filled silastic implant, exposure to short photoperiod was associated with an increase, rather than reduction, in nuclear androgen receptors. The same investigators observed a decline in pituitary nuclear androgen receptors in gonadally regressed hamsters after photostimulation (74). These changes could represent at least one of the mechanisms of photoperiod-related seasonal shifts in sensitivity to androgen feedback.

Suppression of the synthesis and release of pituitary PRL is among the most striking and consistent responses of the neuroendocrine system of the male golden hamster to short photoperiod (38, 46, 66, 75, 76). A reduction in the levels of PRL mRNA in the anterior pituitary was detected 11 days after blinding (77) and is believed to represent the earliest known response of pituitary function to light deprivation.

A reduction in plasma PRL levels and concomitant

reductions in LH and FSH release are responsible for suppression of testicular activity in short photoperiod. The treatment of gonadally regressed hamsters with PRL-secreting ectopic pituitary transplants can restore normal gonadal weight, plasma testosterone levels, and fertility (66, 78). Prolactin elicits these striking responses by increasing both testicular LH binding and plasma levels of LH and FSH (3, 66, 71). The latter effect involves modulation of testosterone negative feedback at both hypothalamic and pituitary levels via mechanisms that include changes in androgen binding in the pituitary (71, 79) and altered responses of noradrenergic and dopaminergic neurons in the hypothalamus to testosterone exposure (14, 48, 71). Unexpectedly, treatment with PRL alone that is started at the time of transferring the animals from a stimulatory to an inhibitory photoperiod is unable to prevent testicular regression from taking place (80), and simultaneous treatment with LHRH is required to maintain testicular weight and function in this situation (81).

Although the suppression of PRL release in short photoperiods was described in many species, including those that breed during short, rather than long, photoperiods (82) or exhibit little or no seasonal fluctuations in fertility (83), the mechanisms responsible for this endocrine response remain to be identified. The release of PRL in mammals is usually controlled by the strength of the inhibitory dopaminergic signal. However, in the male golden hamster, hypothalamic dopaminergic activity is reduced, rather than stimulated, by short photoperiod exposure (40, 44). Examination of the effects of dopamine on pituitary PRL release *in vitro* after various periods of short photoperiod exposure *in vivo* suggested that changes in the sensitivity to dopamine may explain these seemingly inconsistent findings (38). However, this explanation has been questioned (76).

When adult hamsters continue to be exposed to short photoperiods for a prolonged period of time, plasma FSH levels begin to increase after approximately 14 weeks and increases in plasma LH and PRL levels become evident approximately 2 weeks later. These changes are accompanied by a gradual reduction in the sensitivity of LH and FSH release to negative steroid feedback. Increases in plasma gonadotropins and PRL levels can also be induced before the period of spontaneous recovery by exposing gonadally regressed (or regressing) animals to long photoperiods (2, 3). The possible involvement of testicular inhibin in the control of seasonal changes in FSH release remains to be elucidated, since, in the studies of SD-induced testicular regression, both negative and positive associations between plasma FSH and plasma inhibin levels have been reported (84, 85).

Testis

Seasonal suppression of endocrine and spermatogenic functions of the testes in the golden hamster resembles changes observed after hypophysectomy and undoubtedly represents consequences of reduced stimulatory inputs from the pituitary. After 8–12 weeks of short photoperiod exposure, the ability to convert exogenous and endogenous precursors to testosterone is severely compromised, plasma testosterone levels are reduced, and no spermatozoa are released into the epididymis (reviewed in Ref. 3; 86–88). Recent stereological studies documented morphological correlates of suppressed function of both Leydig and Sertoli cells in short photoperiod-exposed animals (89, 90).

Measurements of hormone binding by testicular tissues after various periods of exposure to short photoperiod revealed that atrophy of the testes is accompanied by progressive loss of LH, FSH, and PRL receptors (66, 91, 92). Indeed, reduced testicular LH binding is among the earliest endocrine responses of the male golden hamster to short photoperiod (3). A reduction in the total number of LH and FSH receptors in the testis and in their numbers per Leydig and per Sertoli cell, respectively, is accompanied by increases in their concentrations (per mg of testicular weight), because progressive loss of the germ cells leads to relative enrichment of somatic cells in regressing testes. The loss of PRL and LH receptors appears to be due primarily, if not exclusively, to reduced plasma PRL levels in short photoperiod-exposed animals, because it can be mimicked by selective pharmacologic suppression of PRL release in long photoperiod-exposed hamsters and reversed by treatment with PRL (91). The mechanism(s) responsible for seasonal changes in FSH binding remains to be elucidated.

The biological meaning of reduced LH, FSH, and PRL binding in the regressed testes is not clearly understood. Although the amount of testosterone produced in response to gonadotropic (human chorionic gonadotropin) stimulation *in vitro* is severely reduced in the regressed testes (87, 93), there is no evidence for a shift in the dose-response curve or for an inability to respond to low doses of LH. Sertoli cells isolated from regressed testes exhibit increased responsiveness of adenylate cyclase to FSH stimulation (94, 95). However, profound suppression of testicular function in short photoperiods in spite of a relatively modest reduction in plasma LH and FSH levels makes it tempting to suspect that parallel changes in the levels of gonadotropins and in the number of their gonadal receptors sum up to produce functional suppression of the testes. This speculation appears consistent with the striking stimulation of growth and function of regressed testes by treatment with PRL, which is known to produce rapid recovery of testicular LH binding (3, 66, 78).

Photoperiod-dependent testicular regression in the golden hamster is also accompanied by major changes in the responsiveness of gonadal tissue to catecholamines. Mayerhofer et al. (96, 97) recently reported that epinephrine, norepinephrine, an α-agonist phenylephrine, and histamine do not affect testosterone secretion by incubated testicular tissue from gonadally active hamsters, but produce a significant dose-related increase in the accumulation of testosterone in incubations of tissue from regressed testes. Although the physiological significance of these responses remains to be established, we suspect that stimulation of steroidogenesis by catecholamines may allow the otherwise quiescent testes to release testosterone in response to stress.

There is evidence that testicular regression is accompanied by changes in inhibin production, but the time course of these changes and their physiological significance remain to be elucidated. Using a hamster pituitary cells bioassay, Berkowitz and Heindel (98) reported that Sertoli cells obtained from the testes of blinded, gonadally regressed hamsters produced more inhibin than those obtained from the active gonads of animals maintained in a long photoperiod. These investigators suggested that increased inhibin production, combined with increased responsiveness of the pituitary cells to inhibin, may contribute to the decline in FSH levels during testicular regression (98). Using a radioimmunoassay for measurements of inhibin, we have noted a progressive decrease in serum inhibin levels after 6 and 9 weeks of exposure to short photoperiod, with changes in serum FSH clearly preceding the changes in serum inhibin levels (B. D. Schanbacher and A. Bartke, unpublished observations). In the same study, inhibin levels in the rete testis fluid appeared to be slightly elevated after 4 weeks of exposure to short photoperiod and to decline thereafter. Recent immunohistochemical studies of testicular inhibin content in short photoperiod-exposed hamsters (99) revealed that the number and staining intensity of immunopositive Sertoli cells increased during the initial 6 weeks of exposure and thereafter declined rapidly. Injection of the animals with antiserum to inhibin resulted in a robust increase in plasma FSH levels in animals exposed to short photoperiod for 4 weeks, an attenuated response in those exposed for 6 weeks, and no response in those exposed for 12 weeks (99). The authors concluded that inhibin may be involved in the initial decline in FSH release in response to short photoperiod, while other inhibin-independent mechanisms operate subsequently. Additional studies will be required to clearly establish the cause and effect relationships between the changes in plasma FSH and inhibin levels during the annual gonadal cycle.

Other Hormonal Adaptations

This brief review would be incomplete if we didn't mention that the photoperiod-related seasonal changes in the function of the hypothalamic-pituitary-testicular axis are accompanied by other endocrine adaptations. These include alterations in thyroid and adrenal function (100, 101) (which could affect the release of gonadotropins, PRL, and testosterone by a variety of direct and indirect mechanisms), changes in diurnal rhythms of plasma hormone levels (101), alterations in hormone metabolism (102, 103), and changes in the responsiveness of various target tissues to hormonal stimulation (104). It is also important to realize that changes in the release of "reproductive" hormones, e.g., PRL and testosterone, have consequences unrelated to reproduction, including alterations in body weight and composition, pelage characteristics, food consumption, locomotory activity, and hibernation.

We are beginning to understand some of the neuroendocrine events preceding photoperiod-induced changes in reproductive function in the male hamster, but much additional work is needed. The physiologic response is quite difficult to study, since it appears that many components of the reproductive axis are changing concomitantly. This is not entirely unexpected, since many neuroendocrine control systems readily adapt to experimental perturbation and function quite normally. For example, when noradrenergic neurons responsible for stimulation of LHRH release are destroyed, the normally less dominant DA system appears to assume a more important role in controlling LHRH release.

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