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PHOTOPERIODIC POLYPHENISMS IN RODENTS: NEUROENDOCRINE MECHANISMS, COSTS, AND FUNCTIONS

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This paper is dedicated to Professor Howard A. Bern on the occasion of his 80th birthday.

ABSTRACT

   Annual changes in daylength figure prominently in the generation of seasonal rhythms in reproduction, and a wide variety of mammals use ambient photoperiod as a proximate cue to time critical reproductive events. Nevertheless, within many reproductively photoperiodic mammalian species, there exist individuals—termed "photoperiod nonresponders"—that fail to adopt a seasonal breeding strategy and instead exhibit reproductive competence at a time of year when their conspecifics are reproductively quiescent. Photoperiod nonresponsiveness has been principally characterized by laboratory observations—over half of the species known to be reproductively photoperiodic contain a proportion of nonresponsive individuals. The study of nonresponders has generated basic insights regarding photic regulation of reproduction in mammals. The neuroendocrine mechanisms by which the short-day photoperiodic signal is degraded or lost in nonresponders varies between species: differences in features of the circadian pacemaker, which provides photoperiodic input to the reproductive neuroendocrine system, have been identified in hamsters; changes in the respon-

siveness of hypothalamic gonadotrophs to melatonin and as-yet-unspecified inhibitory signals have been implicated in voles and mice. Individuals that continue to breed when their conspecifics refrain might enjoy higher fitness under certain circumstances. Statements regarding the adaptive function of reproductive nonresponsiveness to photoperiod require additional information on the costs (metabolic and fitness) of sustaining reproductive function during the winter months and how these costs vary as a function of environmental conditions. Reproductive nonresponders thus continue to represent a challenge to theories that extol the adaptive function of seasonality. Several nonexclusive hypotheses are proposed to account for the maintenance of nonresponsive individuals in wild rodent populations.

In looking at many small points of difference between species, which, as far as our ignorance permits us to judge, seem to be quite unimportant, we must not forget that climate, food, &c., probably produce some slight and direct effect. It is, however, far more necessary to bear in mind that there are many unknown laws of correlation in growth, which, when one part of the organisation is modified through variation, and the modifications are accumulated by natural selection for the good of the being, will cause other modifications, often of the most unexpected nature (Darwin 1859).

M ANY SEASONALLY BREEDING species of small mammals use ambient daylength (photoperiod) as a cue to terminate reproduction, but a proportion of individuals forego this species-typical approach to reproduction and instead attempt to breed throughout the year. Darwin's catch-all statement above accepts the notion that phenotypic variance is a consequence of selection by forces both dramatic and sublime, and may well yield unexpected (to the human observer) phenotypes. Such is the nature of the "problem" presented by so-called photoperiod nonresponders. Why do seasonal changes in daylength fail to inhibit the reproductive neuroendocrine axis in just a few individuals? We review the phenomenology and mechanisms that underlie reproductive nonresponsiveness to daylength in rodents and attempt to account for its maintenance in wild and domestic populations. The study of photoperiod nonresponsiveness yields insights into both the physiological mechanisms of photoperiodism and the adaptive significance of seasonal breeding.

In nonequatorial regions, more mammalian offspring are born during the spring than any other time of year (Bronson 1989). The severe energetic cost of the reproductive effort, especially in female mammals, may function as an important ultimate factor that restricts reproduction such that parturition coincides with times of moderate temperatures and accessibility to high-quality food, resulting in relatively less energy expenditure (Clarke 1981; Bronson 1989). It is generally accepted that the accurate temporal orientation of reproduction is a target of natural selection and has

played a major role in the evolution of seasonality (Bronson and Heideman 1994).

Seasonal patterns of reproduction in the wild ultimately obtain their periodicity from annual environmental changes in temperature and food availability, which dictate primary energy availability in a local environment (Bronson 1989). In the majority of cases, however, seasonal trends in reproduction are not simply passively driven by permissive environmental variables, but instead are the product of endogenous timing mechanisms that have evolved to match approximately the annual geophysical periodicity. Two distinct seasonal timekeeping mechanisms regulate reproduction in mammals, both of which result in patterns of seasonal breeding that have a period of approximately 12 months (Zucker et al. 1991). The first type of annual timing mechanisms—"circannual" reproductive rhythms—are endogenous oscillations that persist under constant environmental conditions with a period that deviates slightly from 12 months (usually <12 months). These rhythms restrict reproduction to one phase of the annual cycle by driving changes in metabolism (e.g., lipid mass, hibernation) and reproductive physiology (GnRH content, LH secretion, testis size) (Dark et al. 1984; Dark and Zucker 1985; Gwinner 1986; Dark et al. 1990; Xiong et al. 1997). This class of seasonal rhythm (also known as a Type II rhythm) is typically associated with larger, longer-lived species (e.g., ground squirrels, *Spermophilus lateralis*; Soay rams, *Ovis aries*). Under field conditions, seasonal changes in daylength entrain circannual reproductive rhythms to a period of exactly one year (Zucker

1985; Lee and Zucker 1991). Changes in daylength figure prominently in the *entrainment* of circannual rhythms, but true circannual rhythms persist under fixed daylengths and are thus *generated* independently of fluctuations in ambient photoperiod (Zucker 1988; Karsch et al. 1989).

The second type of annual timing mechanism—"mixed" (or Type I) reproductive rhythms—are a result of the combined activity of: (1) the inhibitory influence of exogenous daylength signals, and (2) an endogenous "semi-circannual" interval timer. In a number of different species of long-day breeding rodents (e.g., mice, hamsters, voles), short daylengths (typically <12.5 h light/day, 12.5L) induce a suite of changes in physiology—decreases in testis and ovarian function, a relative absence of sex behaviors—the net effect of which is to suppress breeding for several consecutive winter months (Bittman 1985; Goldman and Nelson 1993). This maintenance of reproductive involution under short days is not indefinite, but instead is terminated after approximately 20 weeks by an endogenous timing mechanism. Thus, after prolonged exposure to inhibitory photoperiods, long-day breeding rodents spontaneously revert to a reproductively competent (i.e., long-day) phenotype (Reiter 1969; Reiter 1972; Watson-Whitmyre and Stetson 1988). Such "spontaneous recrudescence" is postulated to be a consequence of refractoriness (acquired insensitivity) to short days and their endocrine sequelae. Thus, long-day breeders undergo reproductive involution in response to the decreasing daylengths of late summer and autumn and spontaneously resume reproductive function in the late winter, independent of stimulatory spring photoperiods (Clarke 1981; Bronson and Heideman 1994).

Unlike Type II annual rhythms—which are entrained by, but generated independently of, changes in daylength—Type I rhythms are both *entrained* and *generated* by photoperiod transitions. This dependence of Type I rhythms on direct inhibition by short days necessarily restricts analyses of photoperiod nonresponsiveness to species that employ this type of annual timing mechanism to regulate seasonal breeding. Furthermore, laboratory analyses of circannual species reveal few, if any, reproductive nonresponders, that is, individuals that

fail to exhibit a free-running circannual reproductive rhythm under constant environmental conditions (F Karsch and I Zucker, personal communication). Practical and theoretical concerns thus limit this review to consider the mechanisms that attenuate reproductive responsiveness to short days in photoperiodic (Type I) species and thereby promote a nonseasonal pattern of reproduction.

CLASSIFICATIONS OF PHOTOPERIOD RESPONSES

PHOTOPERIODIC REPRODUCTIVE RESPONSE

Photoperiodism is the ability of plants and animals to measure environmental daylength (Nelson 1999). Organisms are considered photoperiodic if changes in daylength are sufficient to direct alterations in a particular trait. Many rodent species inhibit breeding when daylength (number of hours of light per day) falls below some critical minimum during the late summer/early autumn, and a substantial body of evidence now points to the ability of mammals to cue transitions in reproductive events based on changes in ambient daylength (photoperiod). Individuals and species are *reproductively photoperiodic* if changes in daylength (or their neuroendocrine sequelae) alter traits directly involved in successful reproduction. Well over 30 rodent species fit this definition and are classified as reproductively photoperiodic. In long-day breeders, short daylengths typically induce changes in brain synthesis and storage of peptides that regulate reproductive state (i.e., gonadotropin-releasing hormone, GnRH), declines in circulating concentrations of reproductive hormones (lutenizing hormone, LH; follicle-stimulating hormone, FSH), regression of reproductive apparati (ovarian, testis, and accessory gland size), and decreases in gonadal steroid production and reproductive behaviors (e.g., partner preference, sex behaviors) (Goldman and Nelson 1993). The net effect of these short-day induced physiological events is to arrest reproduction, usually commencing in late summer, and to sustain reproductive quiescence throughout autumn and winter (Zucker et al. 1980; Clarke 1981; Bronson 1989). Photoperiodic rodents commonly decrease body mass in order to conserve energy (Iverson and Turner 1974; Wunder et al. 1977; Wolff and Lidicker 1980; Heldmaier and Steinlechner 1981; Pistole and Cranford

1982; Dark et al. 1983; Dark and Zucker 1984a,b; Wunder 1984), and halt androgen-dependent behaviors such as mating, territorial defense, dispersal, and aggressive and agonistic interactions (Jannett 1984; Madison et al. 1984; Prendergast et al. 2001). The stage of development at which a photoperiodic rodent first encounters short days also profoundly alters life history: a small rodent born into increasing daylengths in the spring may achieve adult body size and reproductive maturity at 40–50 days of age. In the same species, decreasing daylengths of late summer and autumn arrest somatic and reproductive development; individuals born after the summer solstice will delay puberty until the following spring, reaching adult body size at 5–7 months of age (Bronson 1985; Forger and Zucker 1985).

PHOTOPERIODIC NONRESPONSE

In several long-day breeding species, a subset of individuals remains reproductively competent during the winter season when the majority of their conspecifics are reproductively quiescent; these individuals have been observed in both the field and the laboratory (Table 1). Voles (*Microtus* sp.), mice (*Peromyscus* sp.), and Siberian hamsters (*Phodopus sungorus*) have served as the most common rodent model systems for genetic and neuroendocrine analyses of short-day nonresponsiveness.

OBLIGATE VS. FACULTATIVE SEASONALITY

The transition between seasonal phenotypes may be facilitated by long-term (e.g., daylength) or short-term (e.g., food availability, ambient temperature) cues, which differ in their predictive value. Long-term cues permit initiation of reproductive transitions well in advance of the onset of favorable environmental conditions. Accurate over evolutionary time scales, long-term cues lack precision on a given year. More proximate, short-term cues, often the environmental conditions themselves, permit less advance preparation, but are inherently more reliable. Reliance on any single cue for the triggering of seasonal transitions defines a species as obligately seasonal only if that cue returns every season. In the case of seasonal reproduction, the fidelity with which any single environmental cue (e.g., daylength) has predicted future energetic conditions

over the course of recent evolutionary history presumably shaped the extent to which that cue presently regulates reproduction. It follows that, where the onset of spring varies little from year to year, daylength is highly predictive, and seasonally breeding animals should be strongly photoperiodic (Farner 1985; Bronson 1989).

Nevertheless, facultative regulation of reproduction exists in a number of species traditionally touted as obligately photoperiodic. For example, in the California vole (*Microtus californicus*), supplemental green food attenuates gonadal regression in short days (Nelson et al. 1983), as does low humidity in the Kusu rat (*Arvicanthis niloticus*; Sicard et al. 1993). Heterosexual social cues attenuate or prevent gonadal regression in deer mice and Siberian hamsters, respectively (Whitsett and Lawton 1982; Hegstrom and Breedlove 1999). The occurrence of such cues in the wild could modulate or even override seasonal reproductive quiescence.

Seasonal reproductive quiescence is an adaptive reproductive strategy if, in certain environments, breeding at energetically challenging times of year confers lower fitness relative to deferring reproduction until more permissive environmental conditions return. Thus, *when* to breed is as crucial to fitness as *whether* to breed (Bronson 1989; Bronson and Heideman 1994). According to this notion, photoperiod-induced reproductive cessation reflects an adaptive response to the energetic challenges of autumn and winter. Though reproductive regression appears to be the modal response to short photoperiods, the abundant interspecific evidence for photoperiod *non-responsiveness*—in both field and laboratory settings—renders the question of why some individuals fail to respond reproductively to changes in daylength a major challenge to the study of photoperiodism. An adequate treatment of this issue should consider both the ultimate factors that shape reproductive physiology (e.g., fitness associated with seasonal vs. nonseasonal reproductive strategies), and the proximate mechanisms that influence photoperiod effects on reproduction. The next sections review physiological mechanisms by which photoperiod influences reproduction in photoperiodic species and fails to do so in

TABLE 1

Rodents for which reproductive nonresponsiveness to short photoperiod has been demonstrated

Species (common name)	Evidence for nonresponsiveness to photoperiod	Reference(s)
Acomys cahirinus (Egyptian spiny mouse)	Many males do not reduce spermatogenic activity in 10L.[1]	El-Bakry et al. 1998
Arvicanthis niloticus (Kusu rat, Nile rat)	Low humidity inhibits short-day gonadal stimulation.[1]	Sicard et al. 1993
Gerbillus andersoni (Anderson's gerbil)	Many males do not reduce spermatogenic activity in 10L.[1]	El-Bakry et al. 1998
Gerbillus pyramidum (pyramid gerbil)	Many males do not reduce spermatogenic activity in 10L.[1]	El-Bakry et al. 1998
Meriones hurrianae (Indian desert jird)	Estrous cycles persist in some females housed in LL.[2]	Sinhasane and Joshi 1997
Meriones unguiculatus (Mongolian gerbil)	Some males do not regress testes in DD.[1]	Moos et al. 1979
Mesocricetus brandti (Turkish hamster)	47% of females raised in 12L do not delay first vaginal estrus.[2]	Ogilvie and Stetson 1990
Microtus agrestis (field vole)	Some males sustain developed testes in short days.[2]	Baker and Ranson 1932
Microtus arvalis (common vole)	Some males do not regress testes under winter photoperiods.[1,2]	Lecyk 1962
Microtus californicus (California vole)	Green food attenuates gonadal regression in 10L.[1]	Nelson et al. 1983
Microtus montanus (montane vole)	Some females do not reduce litter size in 6L.[1]	Pinter and Negus 1965
Microtus ochrogaster (prairie vole)	>80% of short-day females conceive litters. Some males do not regress testes in short days.	Nelson 1985a
Microtus pennsylvanicus (meadow vole)	A minority of males sustain spermatogenesis under 10L.[2] Some males do not regress testes during winter.[3]	Christian 1980; Dark et al. 1983; Kerbeshian et al. 1994
Perognathus penicillatus (desert pocket mouse)	Estrous cycles persist in some females housed in winter photoperiods.[2]	Ostwald et al. 1972
Peromyscus leucopus (white-footed mouse)	50% of females remain in breeding condition in constant darkness.[2]	Whitaker 1940
Peromyscus maniculatus (deer mouse)	Males undergo gonadal development raised from birth in 6L.[2] Year-round breeding in the field.[3]	Scheffer 1924; Whitsett and Lawton 1982
Phodopus sungorus (Siberian hamster)	Males undergo gonadal development raised from birth in 6L.[2] Individuals in reproductive condition during the winter.[3]	Hoffmann 1978
Rattus norvegicus F344 (laboratory rat, Fischer 344 strain)	Some males exhibit normal gonadal development in short days.[2]	Heideman and Sylvester 1997
Sigmodon hispidus (cotton rat)	Some females maintain perforate vagina in short days.[2]	Johnston and Zucker 1979

Notes: [1] Inferred overlap between long-day and short-day responses based on extrapolation of published data (mean ± 1 SD). [2] Extrapolations based on published data indicating individual animals' responses to photoperiod manipulations. [3] Denotes field observations of winter breeding. DD = continuous darkness; LL = continuous illumination; xL = x hours of light per day.

nonresponsive individuals. Ultimate considerations will be revisited at the conclusion of this review, in light of the proximate mechanisms by which nonresponsiveness is mediated.

MECHANISMS OF PHOTOPERIODIC TIME MEASUREMENT

NEUROENDOCRINE SIGNAL TRANSDUCTION

Information about seasonal changes in daylength enters the neuroendocrine axis via a well-defined retinal-hypothalamic-pineal pathway (Moore 1996). Briefly, the environmental photoperiod entrains circadian oscillators, which in turn regulate synthesis of melatonin from the pineal gland (Illnerova et al. 1984; Elliott and Tamarkin 1994). Pineal melatonin is secreted exclusively at night, and in direct proportion to the duration of the scotophase. A series of successive nightly melatonin signals is decoded by target tissues that regulate seasonal changes in pituitary gonadotropic activity. The duration of the nightly melatonin signal is the critical parameter influencing reproductive function: long-duration (≥8 h/night) melatonin signals cause gonadal regression, whereas short-duration (≤6 h/night) signals stimulate FSH and LH secretion, promoting gonadal development (Carter and Goldman 1983; Bittman and Karsch 1984; Goldman et al. 1984; Bartness et al. 1993).

Long-duration melatonin signals suppress reproductive physiology by inhibiting anterior pituitary gonadotropin secretion (Goldman and Nelson 1993). To date, most neural investigations in rodents have focused on the gonadotrophin-releasing hormone (GnRH) neuronal system as the level of the hypothalamic-pituitary-gonadal axis responsible for modulating the effects of photoperiod on reproductive physiology. The results of these studies are equivocal and, when differences are observed, the magnitude of any differences between long and short-day animals is small. In Syrian and Siberian hamsters, an increase in the number of hypothalamic GnRH-immunoreactive (GnRH-ir) neurons in short days has been noted (Ronchi et al. 1992; Bernard et al. 1999). However, other studies on Siberian and Syrian hamsters have reported no differences in GnRH neuron numbers between long and short-day animals (e.g., Bittman et al. 1991; Urbanski et al. 1991; Yellon 1994; Bittman et

al. 1996). Conceivably, short-day groups in previous studies of Siberian and Syrian hamsters consisted of both responder and nonresponder phenotypes, and this could have accounted for the discrepant findings seen within species and between studies.

When photoperiodic alterations in the GnRH system are observed, increases in neuron numbers are typically associated with the anterior and lateral hypothalamus, preoptic area, diagonal band of Broca, and septal regions (Ronchi et al. 1992; Bernard et al. 1999; Kriegsfeld and Nelson 1999). The degree to which a particular brain region is associated with alterations in GnRH-ir neuronal numbers appears to be correlated with species differences in regional distribution of GnRH neurons. For example, in Syrian hamsters, more rostral brain regions (i.e., medial septum and diagonal band) are associated with increased neuronal numbers (e.g., Ronchi et al. 1992). In contrast, in prairie voles, deer mice, and white-footed mice, more caudal GnRH cell populations (preoptic area and anterior hypothalamus) appear to be affected by inhibitory daylengths (Glass 1986; Korytko et al. 1995, 1998; Kriegsfeld and Nelson 1999; Kriegsfeld et al. 2000a). The extent to which these differences reflect species differences in GnRH cell populations projecting to the median eminence to regulate gonadotropin secretion requires further study.

When differences in the GnRH system are noted between long and short-day animals, increased neuron numbers appear to be the result of decreased GnRH release; the number and density of GnRH-ir fibers extending into the median eminence are increased in animals housed in inhibitory photoperiods (Glass 1986; Ronchi et al. 1992). Increased fiber staining in combination with increased neuron numbers in short-day animals suggests that short photoperiods inhibit reproduction in part by suppressing GnRH release sufficiently to prevent the maintenance of normal gonadal function (Urbanski et al. 1991; Kriegsfeld and Nelson 1999); however, the biological significance of increased GnRH fiber staining in short days is unknown. Studies using immunohistochemistry in conjunction with in situ hybridization to evaluate the additive effects of proximate seasonal cues (temperature, photoperiod) indicate that a single inhibitory proximate factor

(i.e., short daylengths or low temperatures) alone inhibits reproduction by inhibiting GnRH release, whereas concomitant exposure to both factors inhibits reproduction by inhibiting GnRH synthesis as well as GnRH release (Kriegsfeld et al. 2000a,b). Animals in nature may deploy different mechanisms during mild versus harsh winters to suppress reproductive behavior and physiology. In the case of photoperiod nonresponders, individuals that maintain reproductive competence during harsh winters may represent a subset of animals that are insensitive to even multiple convergent winter cues (Desjardins and Lopez 1983).

CENTRAL SITES MEDIATING REPRODUCTIVE RESPONSES TO MELATONIN

In order for short days to affect gonadotropin secretion, melatonin must ultimately either suppress GnRH secretion, attenuate its activity in the pituitary, or reduce gonadal responsiveness to gonadotropins (or a combination of these processes). Current notions as to whether daylength or melatonin can modulate pituitary responsiveness to GnRH are inconsistent and conflicting (e.g., Martin et al. 1977; Jetton et al. 1994). In vivo (Turek et al. 1977; Pickard and Silverman 1979; Bacon et al. 1981; Boyd 1987) and in vitro (Steger et al. 1983; Steger and Gay-Primel 1990; Jetton et al. 1991, 1994) studies in rodents tend to indicate little role for daylength or melatonin in modulating pituitary responsiveness to GnRH, whereas studies in ruminants point to a significant modulatory role for photoperiod signals (Fowler et al. 1992; Xu et al. 1992). It is presently unknown whether melatonin affects GnRH neurons directly or indirectly. Some overlap exists between brain nuclei that bind melatonin and those that contain GnRH neurons (Glass 1986; Glass and Dolan 1988; Korytko et al. 1995).

Brain areas that mediate the reproductive effects of melatonin have been characterized largely based on studies in Syrian and Siberian hamsters. Among hypothalamic nuclei high in ^{125}I-iodomelatonin binding, lesions of the mediobasal hypothalamus (MBH) or the dorsomedial nucleus of the hypothalamus (DMN) eliminate the gonadal response to long-duration daily melatonin infusions in Syrian hamsters (Maywood and Hastings 1995; Maywood et al. 1996). Lesions of the suprachiasmatic

nuclei (SCN) spare this response to inhibitory melatonin treatments in Syrian hamsters (Bittman et al. 1989), but abolish it in Siberian hamsters (Bittman et al. 1991). Microdialysis infusions of melatonin directly into the SCN, reunions nuclei, or the paraventricular nucleus of the thalamus are sufficient to induce gonadal regression in male Siberian hamsters (Badura and Goldman 1992). Brain regions critical to the translation of photoperiod-induced changes in melatonin into changes in gonadotropin secretion appear localized to the medial basal hypothalamic region in rodents, but likely vary among species. Little is known about interactions between these sites of melatonin binding in the induction or maintenance of gonadal regression in response to short days. Interestingly, lesions of the mediobasal hypothalamus spare the lactotropic (i.e., prolactin; PRL) response to long-duration melatonin infusions and short photoperiods in Syrian hamsters, indicating that melatonin signals are transduced into the hypothalamo-pituitary axis via multiple, parallel pathways which may be trait-specific (Maywood and Hastings 1995). In Siberian hamsters, short days may influence prolactin through multiple, melatonin-dependent and independent pathways as well (Bartness et al. 1991; Bittman et al. 1991).

LOSS OF SHORT-DAY PHOTOPERIOD INFORMATION

Photoperiodic influences on reproduction represent an information processing pathway in which a light signal is converted into a gonadotrophic signal. The duration of nightly melatonin secretion is a consequence of a rhythm of pineal melatonin secretion, driven by a circadian clock entrained to the ambient photoperiod. The effects of melatonin on gonadotropin secretion are mediated by high-affinity membrane-bound melatonin receptors in the hypothalamus and perhaps the pars tuberalis. Failure to undergo gonadal involution in short daylengths reflects a degradation or loss of the short-day information at some stage in this information processing pathway. Loss of the short-day signal in nonresponders could be mediated by alterations in the circadian clock that discriminates long from short days (a pre-pineal process). Alternatively, modification within the pineal gland (e.g., melato-

1. Pre-pineal (circadian control of pineal activity)
2. Pineal depletion
3. Post-pineal (hypothalamic target tissue insensitivity)
4. Post-hypothalamic (pituitary target tissue insensitivity)
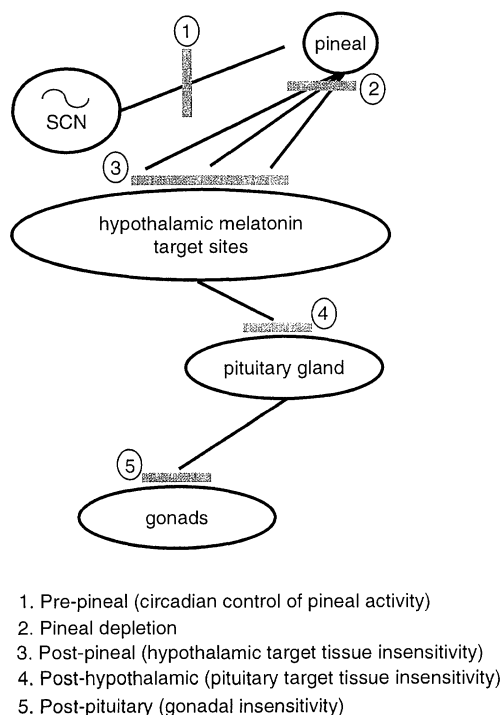5. Post-pituitary (gonadal insensitivity)

FIGURE 1

Schematic representation of neuroendocrine levels at which impairments in short-day signal processing could result in reproductive nonresponsiveness to short photoperiods.

nin depletion), changes in responsiveness of melatonin target tissues, changes in pituitary responsiveness to GnRH, or loss of gonadal responsiveness to LH and FSH (all post-pineal processes) might be implicated (Figure 1).

PHYSIOLOGICAL ANALYSES OF PHOTOPERIOD NONRESPONSIVENESS

UNMASKING LATENT RESPONSIVENESS TO PHOTOPERIOD

A species is operationally regarded as reproductively photoperiodic if it responds reproductively to changes in daylength. Some reproductively photoperiodic rodents respond to changes in daylength only if ancillary factors permit (i.e., under "permissive conditions"). For the present classification, species are regarded as reproductively photoperiodic if such permissive factors represent reasonable ap-

proximations of conditions that occur in the animal's natural habitat. Food restriction, for example, induces gonadal regression in male Syrian hamsters and renders female hamsters anovulatory, causing them to be reproductively unresponsive to the stimulatory effects of long-day photoperiods (Eskes 1983; Schneider and Wade 1989). These species are still considered photoperiodic, however, because under conditions of ad libitum food access—the modal laboratory paradigm—individual Syrian hamsters respond robustly to photoperiod. An assumption with this model is that ad libitum access to high-quality food represents conditions that occur commonly in the wild, although this may not be the case. The extent to which permissive environmental factors can modulate or override reproductive responses to photoperiod has received only limited study, but influences of food quality, temperature, humidity, and social interactions on reproductive responsiveness to photoperiod appear in the literature. Consideration of whether a nonphotic variable permissive for photoperiodic responsiveness reasonably approximates potential field conditions should factor into the interpretation of environmental influences on reproduction and the resultant classifications of a species as photoperiodic or nonphotoperiodic. Arvicanthis niloticus, for example, exhibit robust reproductive responses to short days under certain conditions of temperature and humidity. It seems reasonable to classify this species as photoperiodic because such conditions (high humidity, low T_a) commonly occur in its native west Africa (Sicard et al. 1993).

Laboratory strains of rats (Rattus norvegicus) and mice (Mus musculus) are traditionally considered to be reproductively unresponsive to photoperiod (Nelson and Zucker 1981; Nelson et al. 1994). Failure of Mus to respond to photoperiod has been hypothesized to reflect a lack of functional melatonin production (Ebihara et al. 1986, 1987). Examination of 36 inbred strains of mice indicated only five (C3H/He, CBA/Ms, Mol-A, Mol-Nis, MOM) that displayed significant pineal melatonin production (Goto et al. 1989); the remaining 31 strains, including C57BL/6J, failed to produce nocturnal pineal melatonin. In the case of the C57BL/6J strain, a genetic analysis sug-

gested that mutations in two independently segregating autosomal recessive genes were responsible for the lack of melatonin production. Neither N-acetyltransferase (NAT) nor hydroxy-indole-O-methyltransferase (HIOMT), enzymes necessary for the conversion of serotonin to melatonin, were detected in the pineal glands of C57BL/6J mice (Ebihara et al. 1986). Recently, however, high pressure liquid chromatographic analyses have revealed a brief peak of melatonin in the middle of the night in C57BL/6 and BALB/c strains of inbred mice (Conti and Maestroni 1996). Thus these mice appear to synthesize melatonin; a nighttime peak, albeit a small peak as compared to photoperiodic species, in melatonin production has also been confirmed by radioimmunoassay from pineal samples obtained every 15 minutes throughout the day. The reduction in nighttime melatonin peak in C57BL/6 mice appears to reflect suboptimal NAT function in this strain, rather than a complete absence (Vivien-Roels et al. 1998). A direct comparison among Asian, European, and North American strains of C57 mice may resolve this discrepancy in melatonin values. Rather than a laboratory anomaly, nonresponsiveness in mice may be a characteristic of the genus *Mus* as a whole; even wild mice do not show evidence of reproductive responsiveness to photoperiod (Bronson 1979; Pandey and Pandey 1990).

The failure of laboratory mice and rats to respond reproductively to short days can also be attributed to post-pineal processing of photoperiodic information. Rats and some strains of *Mus* secrete melatonin in a manner similar to that of photoperiodic rodents (i.e., at night and in proportion to the duration of the scotophase; Illnerova and Vanecek 1980, 1988), yet they do not exhibit gonadal regression in short days, and chronic pharmacological melatonin treatments do not affect the testes (Turek et al. 1976). In those species of rats and mice that do produce a nightly melatonin rhythm, the absence of a reproductive response suggests a functional inadequacy in either melatonin signal processing, or positive masking by unspecified mechanisms.

Vestiges of reproductive responsiveness to photoperiod are revealed in typically nonphotoperiodic rats and mice after surgical intervention. For example, in the CF1 strain of house mice and several albino and pigmented strains of rats, at least four different experimental treatments unmask occult reproductive responsiveness to photoperiod: (1) perinatal testosterone injection (Vanecek and Illnerova 1982; Nelson 1990), (2) chronic peripubertal exposure to testosterone (Wallen and Turek 1981), (3) peripubertal removal of the olfactory bulbs (Nelson and Zucker 1981; Nelson 1990; Nelson et al. 1994), and (4) moderate restriction of food intake (Sorrentino et al. 1971). Each of these treatments reduced reproductive organ size and function in animals exposed to short, but not long, photoperiods. In all four paradigms, prior removal of the pineal gland blocked reproductive responsiveness to short days. The physiological mechanisms through which early testosterone treatment or olfactory bulbectomy unmasks reproductive responsiveness to photoperiod remain unspecified, but presumably involve the organization or activation of the neural circuitry underlying photoperiodism.

Because rats and mice exhibit gonadal regression when challenged with short photoperiod only if first olfactory bulbectomized or treated perinatally with testosterone (Wallen et al. 1987; Nelson 1990; Nelson et al. 1994), and such manipulations are highly unlikely to occur in the field, these species/strains are not regarded as reproductively photoperiodic. However, recent studies have revealed that some strains of rats, notably Fisher 344, retain modest reproductive responsiveness to photoperiod (Leadem 1988; Heideman and Sylvester 1997). The physiological differences that may account for the reproductive responsiveness to photoperiod between Fisher 344 rats and other strains of rats remain unspecified. Similarly, the extent to which nonresponsive strains of rodents reflect the parental species response to photoperiod has not been adequately evaluated.

NONRESPONSIVE PHENOTYPES

As described in Figure 1, physiological changes that result in a functional loss of the short-day photoperiod signal may occur at any stage between photoperiod input and gonadal target tissues. Laboratory studies of reproductive nonresponsiveness have described neuroendocrine features that distinguish photo-

TABLE 2

Intrinsic and extrinsic factors that influence reproductive nonresponsiveness to short photoperiods in rodents,
and the neuroendocrine level at which the short-day photoperiod signal is lost

Species	Intrinsic determinants	Extrinsic determinants	Neuroendocrine level(s)
Siberian hamster (*Phodopus sungorus*)	• Genetic component $0.20 < h^2 < 0.52$ • Age	• Exposure to very long (18L:6D) daylengths. • Access to heterosexual conspecifics.	• Pre-pineal *Circadian $\tau < 24.0$ h* • Post-pineal *Unknown*
Prairie vole (*Microtus ochrogaster*)	• Genetic component *Indirect selection associated with domestication*	*Unknown*	• Post-pineal *Absence of GnRH response to unspecified inhibitory signals (melatonin?)*
White-footed mouse (*Peromyscus leucopus*)	• Genetic component $0.54 < h^2 < 0.74$ • Latitude of origin	*Unknown*	• Post-pineal *Nonresponsiveness to melatonin*
Deer mouse (*Peromyscus maniculatus*)	• Genetic component • Latitude of origin	• Access to heterosexual conspecifics.	• Post-pineal *Nonresponsiveness to melatonin*
Meadow vole (*Microtus pennsylvanicus*)	*Unknown*	• Voluntary exercise.	• Post-pineal *Nonresponsiveness to melatonin*
Syrian hamster (*Mesocricetus auratus*)	• Genetic factors $\tau \ll 24.0$ h » τ	• Voluntary exercise. • Access to heterosexual conspecifics.	• Pre-pineal *Circadian $\tau \ll 24.0$ h or $\tau \gg 24.0$ h*

period responders from nonresponders, in addition to the etiology of such differences. Neural and endocrine differences between responders and nonresponders may be solely a result of *intrinsic* (genetic) factors, or may arise from *extrinsic* (experiential) events.

Photoperiod nonresponsiveness has been examined most thoroughly in four species: Siberian hamsters (*Phodopus sungorus*), prairie voles (*Microtus ochrogaster*), white-footed mice (*Peromyscus leucopus*), and deer mice (*Peromyscus maniculatus*). Intrinsic and extrinsic factors that influence the reproductive response to short daylengths include age, genetic predisposition, latitude of origin, activity level, ambient temperature, social factors, and photoperiodic history. Rather than indicating a common mechanism across photoperiodic rodents, data from these four species suggest that multiple distinct neuroendocrine mechanisms mediate reproductive nonresponsiveness to photoperiod (see Table 2).

Siberian Hamsters (*Phodopus sungorus*)

Siberian hamsters are seasonally breeding cricetid rodents that inhabit the semideserts and arid steppes of continental Asia, an environment characterized by a marked, predictable decline in air temperature and food availability during the fall and winter months (Weiner 1989). The majority of male Siberian hamsters undergo testicular regression after >6 weeks of exposure to short days (<13 h light/day; 13L:11D; Hoffmann 1982). In laboratory populations, approximately 30% of individuals are reproductively unresponsive to short days (Hoffmann 1978, 1979; Puchalski and Lynch 1986). Both genetic and environmental factors influence nonresponsiveness in this species.

Intrinsic Determinants. Bidirectional selection experiments conducted by Lynch and colleagues yielded inbred strains of nonresponder Siberian hamsters (Lynch et al. 1989). Four generations of selection on gonadal regression in short days resulted in >90% nonresponsiveness (Kliman and Lynch 1992). Across several experiments, estimates of heritability ranged from $h^2 = 0.20$ to $h^2 = 0.52$ (moderate to strong; Lynch et al. 1989; Kliman and Lynch 1992). It appears that the principal trait being selected for in these experiments was the period (τ) of the circadian pacemaker (Puchalski and Lynch 1994; Freeman and Goldman
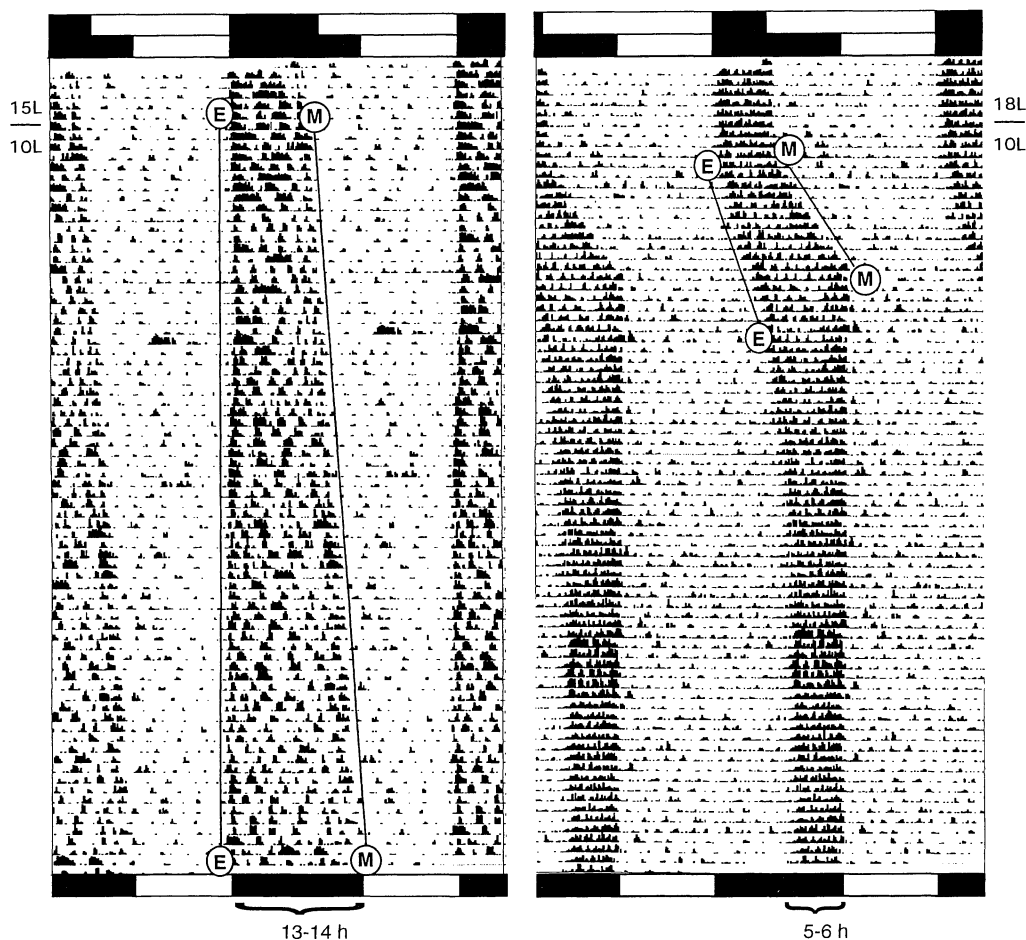
15L
10L

18L
10L

13-14 h

5-6 h

FIGURE 2

Double-plotted circadian locomotor activity rhythms of a photoresponsive (Left) and nonresponsive (Right) male Siberian hamster housed in a short-day photoperiod (10L:14D) beginning on the 7th day of the record. The responsive hamster was previously housed in 15L:9D, whereas the nonresponsive hamster had been kept in 18L:6D. Black-and-white bars at the top of the figures indicate times of dark and light phases, respectively. The upper and lower bars at the top of the figure represent the initial and final photoperiod conditions, respectively; the final photoperiods are also depicted at the bottom of the figure. Overlaid lines depict the approximate position of evening (E) and morning (M) circadian oscillators which control locomotor activity and pineal melatonin secretion. E and M oscillators expand in photoresponsive hamsters, but remain compressed in nonresponders. (Data from Prendergast and Freeman 1999.)

1997a,b). Nocturnal photoperiodic rodents typically expand the duration of nightly locomotor activity (α) upon transfer from long to short days. The duration of α is proportional to the duration of nightly melatonin secretion, both consequences of the entrained phase of the circadian pacemaker (Elliott and Tamarkin 1994). Hamsters that exhibit long (>24 h)

values of τ are reproductively nonresponsive to short days, as long circadian periods result in a pattern of entrainment characterized by a compressed α under short photoperiods (Puchalski and Lynch 1986; Freeman and Goldman 1997a; Figure 2). The short-duration (≤ 6 h/night) melatonin secretory pattern associated with a compressed α is incompatible with

testicular regression in this species (Goldman et al. 1984; Bartness et al. 1993).

The short-day signal transduction pathway is altered at the level of the circadian clock in the SCN in genetic nonresponders (Margraf et al. 1991). Consequently, these animals do not exhibit the normal short-day pattern of entrainment (Puchalski and Lynch 1988). Unlike photoresponsive conspecifics, they generate a melatonin signal in short daylengths that differs little from the normal long-day pattern. In circadian terms, the onset of subjective night (CT12) is phase delayed by at least 4–6 hours, and circadian α and the duration of melatonin secretion are consequently truncated; these animals never "register," or encode their presence in short days. Nonresponder Siberian hamsters are reproductively responsive to exogenous, short-day-like melatonin treatments, indicating that components of the reproductive axis downstream of the pineal gland function normally in these morphs (Puchalski and Lynch 1988).

Extrinsic determinants. Nonresponsiveness to short days can be induced in otherwise responsive hamsters by appropriately timed photoperiod manipulations. In >85% of hamsters, exposure to long daylengths (e.g., 18L:6D) for 10 weeks prevents α from expanding upon subsequent exposure to short days. This results in a compressed rhythm of nightly melatonin secretion that is incompatible with regression of the reproductive apparatus under short photoperiods (Gorman and Zucker 1997; Prendergast and Freeman 1999). Environmentally induced nonresponsiveness is qualitatively similar to genetic nonresponsiveness in that α remains compressed in short days. The mechanisms by which the circadian system is transformed by an episode of 18L:6D, so as to render hamsters unresponsive to short days, remain unknown. Environmental induction of nonresponsiveness is proposed to reflect changes in coupling strength among circadian oscillators. According to one hypothesis, very long photoperiods align evening (E) and morning (M) circadian oscillators in close temporal proximity. These oscillators are responsible for timing the onset and offset of nocturnal melatonin secretion. Coupling strength between these two oscillators is proposed to be increased by their mutual proximity. According to this hypothe-

sis, when coupling strength is sufficiently increased, E and M oscillators get "stuck" such that onset and offset of melatonin secretion occur in close proximity to one another. This change in E-M coupling permanently alters the circadian system. Upon subsequent exposure to short photoperiods, E and M retain their new phase relation; expansion of nightly melatonin secretion does not occur, and hamsters cannot undergo gonadal regression (see Gorman and Zucker 1997).

Temporal proximity of E and M oscillators may be sufficient to induce permanent changes in the circadian system; alternatively, ancillary factors may influence E-M coupling status. Pineal melatonin secretion, thought to influence circadian oscillator interactions under certain conditions of weak coupling (Cassone 1992), does not affect changes in E-M coupling associated with nonresponsiveness: 18L:6D induces nonresponsiveness in intact and pinealectomized hamsters alike (Prendergast and Freeman 1999). Nonresponsiveness is reversed either by manipulations of the circadian system early in life (Freeman and Goldman 1997b), or by prolonged exposure to continuous darkness in adulthood (Freeman and Goldman 1997a). Each of these treatments recalibrates the circadian system and results in an expansion of α and a corresponding expansion of nightly melatonin secretion (Freeman and Goldman 1997a).

Environmental induction of nonresponsiveness by very long daylengths may be of considerable functional significance in the wild. Siberian hamsters that attain reproductive competence prior to the summer solstice in nature are unlikely to survive over winter and breed again in the following summer. A failure to respond to short days with reproductive inhibition may constitute a "go-for-broke" strategy which is usually unsuccessful but infrequently permits successful breeding during mild winters (Gorman and Zucker 1997). Indeed if, because of advanced age, an individual is unlikely to survive over winter, there may be little ecological reason to abandon active breeding condition. It should be noted, however, that laboratory stocks of Siberian hamster have been outbred only infrequently. Circadian abnormalities that mediate the environmental induction of nonresponsiveness have yet to be

described in outbred rodent populations. It may be the case that, in the laboratory, aberrations of the circadian system which permit nonresponsiveness go unchecked by natural selection and render the Siberian hamster a very peculiar laboratory animal model that may be different from the same species living in the wild.

In several rodent species, social cues influence reproductive responses to short days (Whitsett and Lawton 1982). Long-day male hamsters fail to exhibit gonadal regression when paired with a fecund female on the day of transfer to short days. A similar lack of testicular regression is observed if a male is paired with a photorefractory short-day female, suggesting that anomalous patterns of entrainment are unlikely to account for reproductive stimulation by the female (Hegstrom and Breedlove 1999). On the assumption that these males have normal, short-day patterns of melatonin secretion, it appears that social cues such as contact with fecund heterosexual conspecifics masks the inhibitory effects of long-duration melatonin signals. This form of nonresponsiveness differs from the one described above in that responsiveness to the melatonin signal is changed, implicating mechanisms operating at post-pineal sites. Male Siberian hamsters have not been paired with anovulatory short-day conspecific females in this model, which is necessary to establish the importance of female reproductive condition in overriding short-day gonadal regression in males.

Advanced age has been linked to photoperiod nonresponsiveness in Siberian hamsters. Presumably unlikely to survive to breed in the following spring, older individuals risk little residual reproductive value by attempting to breed during the energetically unfavorable fall and winter months. After approximately 1 year of age, a majority of male hamsters fail to undergo gonadal regression when exposed to short days (Bernard et al. 1997). In this study, hamsters were housed in alternating cycles of 16L:8D and 6L:18D; thus advanced age was confounded with increased duration of exposure to long photoperiods, as well as intermittent episodes of exposure to short days, both of which are known to induce nonresponsiveness to short days (Gorman and Zucker 1997; Prendergast et al. 2000). Animals must

be exposed to *some* photoperiod throughout development. Given that long photoperiods induce nonresponsiveness and prolonged exposure to short photoperiods induces refractoriness, it is difficult to experimentally assess the role of advanced age per se in modulating reproductive responsiveness to photoperiod.

Prairie Voles (*Microtus ochrogaster*)

Prairie voles are seasonally breeding arvicoline rodents that inhabit much of the midwestern United States. A majority of prairie voles inhibit reproduction during the winter months or when exposed to short photoperiods (e.g., 8L:16D) in the laboratory (Nelson 1985a; Nelson et al. 1989). Short days cause modest gonadal regression in adult prairie voles. Most juvenile males, however, are highly responsive to photoperiod: testis weights of males raised from birth in short days are nearly 50% lower than those of males reared in long days and fertility is significantly impaired (Nelson 1985a). Approximately 30% of male prairie voles are reproductively nonresponsive to short photoperiods and exhibit complete gonadal maturation despite maintenance from birth in short days (Figure 3; Nelson 1985a, 1987).

Intrinsic Determinants. No intentional efforts have been made to artificially select for reproductive responsiveness to photoperiod in prairie voles; thus the relative contribution of genetic factors to photoperiod responsiveness remains unclear. A strong genetic contribution seems likely, however, based on the observation that responsiveness to photoperiod is lost within a few generations in laboratory populations of prairie voles. Thus, inadvertent selection processes associated with laboratory husbandry can select against reproductive responsiveness to inhibitory photoperiods (Nelson 1985b). When raised from birth in short days, some prairie voles fail to exhibit delayed puberty and exhibit long-day-like reproductive development (Nelson 1985b). This observation suggests a genetic basis for nonresponsiveness to short daylengths (i.e., in a common rearing environment, select individuals do not respond to short days); however, prenatal maternal signals cannot be ruled out as influencing the phenotype, potentially by accelerating postnatal development, as is the case in meadow voles (Lee and Zucker 1988; Lee 1993).
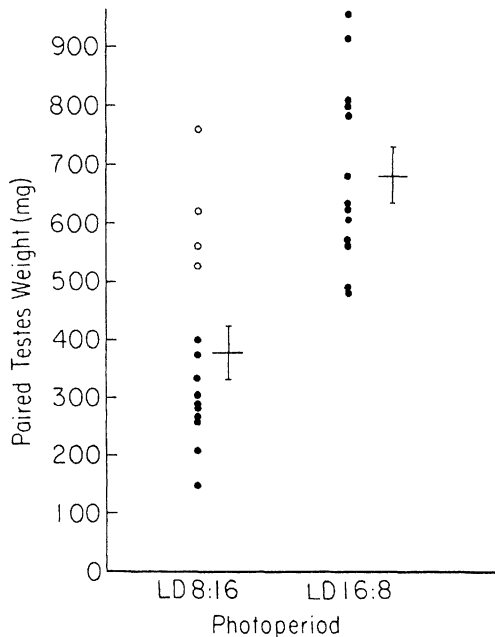
FIGURE 3

Paired testis weights (mg) for individual prairie voles (*Microtus ochrogaster*) after chronic maintenance from birth until 35 days of age in long (16L:8D) or short (8L:16D) photoperiods. Horizontal bars indicate treatment group means (±SEM); solid circles indicate individual values for paired testis mass; open circles indicate testis masses of short-day voles that developed their reproductive systems despite continual exposure to inhibitory photoperiods. (Data from Nelson 1985a.)

Extrinsic Determinants. Voles exhibit marked recurring (year-to-year) fluctuations in population density (Krebs 1966). A diagnostic feature of these population "cycles" are population peaks, declines, and nadirs, over which the numbers of individuals range from 1000 to 0.1 individuals per hectare (Rose and Gaines 1978; Getz et al. 1979). One theory proposes that the proportion of nonresponder morphs in a local population strongly influences population density in the immediate future (Nelson 1987). Implicit in this hypothesis is that population crashes (immediately preceded by population peaks) may be mediated in part by a decline in the number of nonresponders in the population. If population density were capable of influencing photoperiod respon-

siveness, one would predict higher population density to decrease the incidence of nonresponsiveness. At least in prairie voles, population density does not appear to affect reproductive traits, however. Males housed under conditions of high (11 animals/m^3) and low (0.18 animals/m^3) population density exhibited comparable reductions in testis and seminal vesicle weights after exposure to short days for 10 weeks, despite the fact that short-day reductions in traits unrelated to reproduction (adipose tissue and body mass) were strongly attenuated by high population density (Nelson et al. 1996).

Neuroendocrine Mechanisms. The neuroendocrine mechanisms that mediate differential reproductive responses to short photoperiods in prairie voles appear to involve changes in the hypothalamic GnRH neuronal system. Male prairie voles that undergo gonadal regression after 10 weeks in short days exhibited increases in the number of GnRH-ir neurons in the preoptic area/anterior hypothalamus (POA/AH) relative to voles housed in long days (Kriegsfeld and Nelson 1999). Increases in median eminence GnRH-ir fiber-optical density were also associated with the photoregressed phenotype. Nonresponder voles, which failed to exhibit gonadal regression in short days, did not manifest increases in either POA/AH GnRH-ir neuron number or in median eminence GnRH-ir fiber density (Figure 4). Together, these data suggest that short-day nonresponsiveness may be a function of alterations in the response of the GnRH system to signals from the pineal (Kriegsfeld and Nelson 1999).

The role of pituitary responsiveness to GnRH in mediating the phenotypic dimorphism in reproductive responsiveness to photoperiod has also been assessed in prairie voles, as changes in the GnRH-ir neuronal system associated with nonresponsiveness may not be sufficient to entirely mediate the loss of responsiveness to short daylengths. One would predict increased responsiveness of pituitary gonadotrophs to GnRH in nonresponders if changes in pituitary sensitivity contributed to reproductive nonresponsiveness. However, reproductive responses in photoresponsive prairie voles were not associated with differences in pituitary responsiveness to GnRH, nor were deficits in responsiveness to GnRH observed
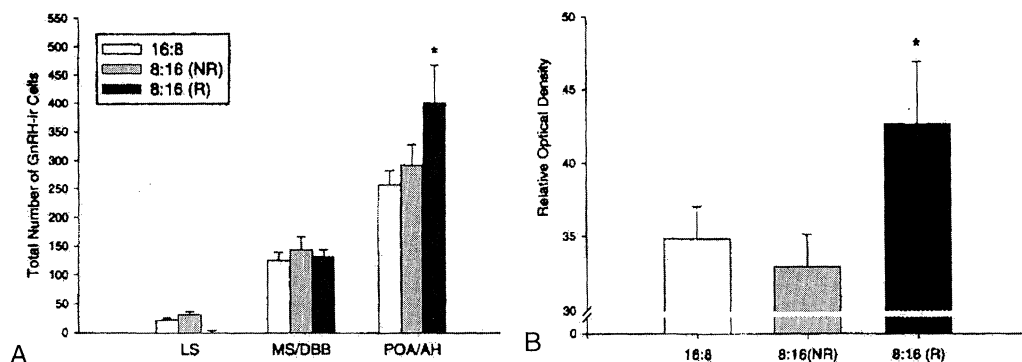
FIGURE 4

(A) Total number of gonadotrophin-releasing hormone-immunoreactive (GnRH-ir) neurons in the brains of male prairie voles (*Microtus ochrogaster*) exposed to long days (16L:8D), or voles maintained in short days (8L:16D) that either responded or did not respond to inhibitory daylengths with reproductive regression. Abbreviations: LS = lateral septum; MS/DBB = medial septal area and diagonal band of Broca; POA/AH = preoptic area and anterior hypothalamus. (*Significantly greater than value of 16L:8D voles). (B) Relative optical density of GnRH-ir fiber staining in the median eminence of male prairie voles housed for 10 weeks in 16L:8D or voles maintained in 8L:16D that either responded (R) or did not respond (NR) to 8L:16D with reproductive regression. *Significantly greater than values for both 8L:16D(NR) and 16L:8D voles. (Data from Kriegsfeld et al. 1999.)

in nonresponders: GnRH-stimulated pituitary LH release was comparable in photostimulated, photoregressed, and nonresponder prairie voles (Kriegsfeld et al. 1999). These data suggest that changes in the hypothalamic GnRH neuron system may be sufficient to mediate the loss of responsiveness to short days in this species.

In summary, reproductive nonresponsiveness to photoperiod in prairie voles is a consequence of changes prior to or at the level of hypothalamic GnRH neurons. Short-day information, as reflected by the number and density of GnRH-ir neurons, is functionally absent by this stage of the neuroendocrine signaling pathway. No attempt has been made to compare nocturnal melatonin rhythms between responder and nonresponder prairie voles; the hypothesis that changes at the level of pineal melatonin production—possibly a consequence of differences in the circadian system (cf. Siberian hamsters)—constitute the primary cause of the observed differences in the GnRH system remains to be explicitly tested. However, even reproductively nonresponsive prairie voles exhibit an appropriate short-day pelage (fur) molt (Smale et al. 1988; Nelson et al. 1989). If

photoperiodic changes in pelage are melatonin-mediated, then it follows that the appropriate short-day pattern of melatonin (i.e., of adequate amplitude and decompressed, relative to long-day patterns) is being released from the pineal gland even in nonresponders. Thus, photoperiod nonresponsiveness in prairie voles appears most likely to be mediated by mechanisms downstream from the pineal gland.

White-Footed Mice (*Peromyscus leucopus*)

Nonresponder white-footed mice were first characterized in laboratory studies (Johnston and Zucker 1980). In most individuals, maintenance in short photoperiods from birth delays sexual maturation, and exposure of adults to short days induces regression of the gonads (Johnston and Zucker 1980; Petterborg and Reiter 1980; Lynch et al. 1981). Some individuals, however, fail to adopt the modal short-day phenotype and instead sustain a substantial degree of gonadal development under short days (Johnston and Zucker 1980; Carlson et al. 1989).

Intrinsic Determinants. The incidence of nonresponsiveness in adult *P. leucopus* varies as a function of latitude of origin. Approxi-

mately 70% of mice trapped at 42°N in Connecticut (CT) are reproductively responsive, whereas virtually all *P. leucopus* trapped at 34°N in Georgia (GA) fail to respond to short days with reproductive regression (Carlson et al. 1989). The magnitude of gonadal quiescence elicited by short photoperiods appears to increase linearly with latitude in both sexes, suggestive of a latitudinal cline in photoresponsiveness (Gram et al. 1982). However, recent work in two northern populations of photoresponsive white-footed mice indicates genetic variation more consistent with a mosaic pattern rather than a latitudinal cline. Estimates of narrow-sense heritability in these populations range from 0.54 to 0.74, and three generations of selection for short-day responsiveness yielded over 80% responders (Heideman et al. 1999a). It is unclear whether nonresponsiveness observed within responsive populations and nonresponsiveness in populations that are nonresponsive as a whole are mediated by common mechanisms.

External Determinants. A role for experiential events (e.g., social factors, photoperiod history) in influencing responsiveness to photoperiod has not been explicitly examined in white-footed mice.

Neuroendocrine Mechanisms. An early study indicated short-day circadian entrainment patterns (τ) and patterns of pineal melatonin content were comparable in responder and nonresponder *P. leucopus*—implicating loss of the short-day signal at some post-pineal level (Carlson et al. 1989). More recent investigations have identified minor differences in the circadian systems of nonresponder white-footed mice; specifically, nonresponder females exhibit a longer free-running τ in constant darkness than do responders. However, this difference in τ does not affect parameters of entrainment, and does not play a causal role in the failure to respond reproductively to short days (Majoy and Heideman 2000). Comparisons of responder and nonresponder mice implicate neuroendocrine differences at some post-pineal level in the mediation of nonresponsiveness (i.e., nonresponsiveness to short-day melatonin signals). Melatonin implants delay sexual maturation and induce gonadal regression in juvenile and adult CT-derived *P. leucopus* (Lynch and Epstein 1976; Petterborg and Reiter 1981;

Petterborg and Reiter 1982), as do daily afternoon melatonin injections (Margolis and Lynch 1981; Heather and Lynch 1982), suggesting that long-duration melatonin signals are sufficient to induce gonadal regression. Afternoon melatonin injections failed to elicit regression in mice from GA, suggesting that nonresponsiveness to melatonin mediates the lack of responsiveness to photoperiod in individuals of the GA population (Heath and Lynch 1982).

A number of studies have examined differences in melatonin receptors between responder and nonresponder *P. leucopus*. Melatonin receptors are distributed throughout the rodent hypothalamus and forebrain (Weaver et al. 1989). Considering our limited knowledge regarding the cellular mechanisms by which melatonin signals are decoded in the brain, either increases or decreases in the number, location, density, or ligand affinity of melatonin receptors might reasonably be expected to covary, along with responsiveness to photoperiod. On this issue, data that associate categorical changes in reproductive responsiveness to photoperiod with changes in melatonin receptors are conflicting and mostly negative (e.g., Mason and Rusak 1990). In one study, CT and GA white-footed mice exhibited comparable distribution and affinity of 2-^{125}I-iodomelatonin (IMEL) binding when assessed under identical long-day conditions (Weaver et al. 1990). Responsiveness to melatonin (as measured by melatonin inhibition of forskolin-stimulated cAMP) also appeared comparable between responder and nonresponder mice. Together these data suggest that the absence of the short-day reproductive response is not a consequence of differences in the number, location, or density of IMEL binding, nor can differences in responsiveness to photoperiod be explained in terms of deficits in second messenger mechanisms in cells bearing melatonin receptors (Weaver et al. 1990). Recent quantitative analyses contradict these assertions, however. Higher binding of IMEL was observed in the medial preoptic area and the bed nucleus of the stria terminalis of nonresponders versus responders raised in short days, implicating changes in the number, binding, or affinity of hypothalamic melatonin receptors associated with the loss of responsiveness to inhibitory photoperiods (Heideman et

al. 1999b). Differences in photoperiod treatments and reproductive state unfortunately preclude reconciling these two studies.

Deer Mice (*Peromyscus maniculatus*)

The extent to which deer mice undergo gonadal regression when exposed to winter conditions or short daylengths (<12.5 h light/day; Stebbins 1977; Whitsett and Miller 1982; Ruf 1993) depends on latitude of origin (Gram et al. 1982; Dark et al. 1983), ambient temperature, and availability of food (Demas and Nelson 1998), as well as a genetic polyphenism that renders animals nonresponsive to inhibitory patterns of melatonin secretion (Desjardins et al. 1986). In deer mice trapped in North America, approximately one-third of the population responds to short days with gonadal regression (testis sizes are reduced by $>80\%$); another third is reproductively unresponsive to short days (gonadal function continues normally), and the remaining animals exhibit an intermediate response to short days, characterized by a slight ($35–45\%$) reduction in testis size and intermediate levels of testicular activity (Blank and Desjardins 1986; Ruf et al. 1997). Differences in reproductive responsiveness to photoperiod are also reflected by changes in sperm number, weight of accessory glands, plasma concentrations of gonadotropins, and features of the GnRH neuronal system (Dark et al. 1983; Blank 1992; Korytko et al. 1995).

Intrinsic Determinants. As described above, in outbred laboratory populations, one-third of the deer mice are reproductively nonresponsive to short days. Latitude of origin influences the incidence of reproductive responsiveness to both short-day photoperiods and melatonin implants in deer mice. In juveniles of this species, a latitudinal gradient of nonresponsiveness has been described: nonresponders comprised 50%, 27%, and 0% of deer mice derived from 27°, 44°, and 55°N, respectively (Dark et al. 1983). Adult males from Chihuahua, Mexico (27°N), were unresponsive to short photoperiods that effectively induced gonadal regression in mice from South Dakota (44°N). Treatment with subcutaneous melatonin implants yielded an identical pattern of responsiveness, suggesting that latitudinal differences in responsiveness to photoperiod are mediated by differences in responsiveness to melatonin (Dark et al. 1983).

A substantial genetic component influences photoperiod nonresponsiveness in this species. As few as two generations of directional selection on photoperiod nonresponsiveness yields strains of deer mice in which $>80\%$ or $<20\%$ of individuals are short-day nonresponders (Desjardins et al. 1986). The proportion of nonresponders in wild populations of deer mice may undergo rapid changes in years when environmental variables permit successful autumn or winter breeding.

Extrinsic Determinants. Social cues influence reproductive responsiveness to short days in juvenile deer mice. Maintenance in short days from birth typically retards gonadal development for 5–6 months in male deer mice; however, cohabitation with an adult female is associated with substantial maturation of the testes and seminal vesicles (Whitsett and Lawton 1982). Thus, as is the case in Siberian hamsters, social interactions with a heterosexual conspecific can override the inhibitory effects of short daylengths in deer mice. The neuroendocrine level at which positive masking from conspecific cues occurs has not been investigated. It is also unknown whether photoperiod history influences reproductive responsiveness to photoperiod in deer mice.

Neuroendocrine Mechanisms. Nocturnal melatonin rhythms, as reflected in pineal melatonin content and patterns of urinary 6-sulphatoxy-melatonin excretion, are comparable in photoperiod-responsive and nonresponsive deer mice. Phenotypic differences are therefore unlikely due to differences in pineal melatonin biochemistry or secretion (Blank et al. 1988; Ruf et al. 1997). Deer mice that vary in reproductive responsiveness to short days are not equally responsive to melatonin. Spermatogenesis was suppressed by melatonin implants in deer mice responsive to short days (based on a prior episode of gonadal regression in short days), whereas melatonin had no effect on the testes of nonresponders. Identical patterns of pineal melatonin secretion in short days appear to be decoded differently by unspecified post-pineal mechanisms. Loss of reproductive responsiveness to short daylengths in deer mice appears to involve changes in responsiveness to normally inhibitory melatonin signals (Blank and Freeman 1991).

In deer mice, differences in the GnRH-ir

neuronal system are associated with divergent reproductive responses to short days (Korytko et al. 1995). Deer mice that undergo gonadal regression in short days exhibit increases in the number, area, or optical density of GnRH-ir neurons in the anterior hypothalamus (AH), diagonal band of Broca (DBB), lateral hypothalamus, preoptic area (POA), medial basal hypothalamus (MBH), and medial preoptic area (MPOA). In nonresponder deer mice, some brain regions (lateral POA) adopt a short-day GnRH-ir phenotype, whereas other regions (lateral hypothalamus) remain unaffected by short photoperiods and maintain the long-day GnRH-ir phenotype; still other regions (DBB, MPOA) manifest a GnRH-ir pattern that resembles neither the long nor short-day pattern (Figure 5; Korytko et al. 1995). Furthermore, increases in GnRH accumulation under short days are steroid-dependent in some brain regions, but not in others (Korytko et al. 1997, 1998).

The presence of hypothalamic sites at which short-day nonresponders manifest the long-day GnRH-ir phenotype suggests that short-day information is lost prior to the level of the pituitary gland. Some groups of GnRH neurons, however, adopt a normal short-day phenotype in reproductively nonresponsive deer mice (Korytko et al. 1995), pointing to a complex interaction between melatonin and GnRH-ir neurons in the mediation of nonresponsiveness. One possibility is that short-day information gains access to GnRH neurons in some of these regions (those that adopt a short-day GnRH phenotype) but not in others.

The relative contributions of each subgroup of GnRH neurons to the integrated testicular response are presently unknown (i.e., which populations of GnRH neurons are necessary and sufficient for gonadal regression to occur); however, the pattern of GnRH-ir observed in nonresponders suggests that subpopulations of GnRH neurons in the AH, lateral hypothalamus, and the MBH mediate the short-day reproductive response: the GnRH phenotypes in these three regions were comparable in short-day nonresponders and long-day mice (Korytko et al. 1995). Because the signal at the level of GnRH content differs between short-day responders and nonresponders, some short-day information is either lost or has deterio-

rated prior to or at the level of GnRH neurons. Whether these changes are sufficient to mediate nonresponsiveness to daylength, or whether signals downstream in the hypothalamic-pituitary-gonadal axis are also implicated, awaits further analyses. The GnRH system represents a neural locus for the integration of photoperiodic signals into the reproductive axis, though it may not be the only level at which short day information is lost in deer mice.

As is the case in prairie voles, photoperiod nonresponsiveness in deer mice is trait-specific. Plasma PRL concentrations in reproductive nonresponder deer mice are fully responsive to short days, decreasing to values indistinguishable from those of reproductively responsive mice in short days (Blank and Desjardins 1986). Reproductive nonresponder deer mice exhibit increases in nonshivering thermogenesis and maximum heat production (usually referred to as "nonreproductive" traits) after exposure to short days, further indicating that adequate short-day signals are being generated by the neuroendocrine system (Blank and Ruf 1992). Short-day signals sufficient to modulate some photoperiodic traits are transmitted to the pituitary gland and other metabolic effector systems, even as others retain the long-day phenotype. This dissociation underscores the notion that it is more appropriate to designate traits, rather than individuals, as nonresponsive to daylength (Nelson 1987; Zucker 1988).

Meadow Voles (*Microtus pennsylvanicus*)

Meadow voles inhabit most of the eastern United States and are found as far west as Illinois. The voles are highly polygynous and their distribution overlaps with *M. ochrogaster* from Ohio westward. Importantly, meadow voles display strong patterns of seasonal breeding in the field (Krebs et al. 1973; Kerbeshian et al. 1994), and are highly photoperiodic in the laboratory (Imel and Amann 1979). When maintained in short days in the laboratory, some individuals undergo complete gonadal regression, some individuals display no gonadal regression, and other individuals display intermediate responses. A sample of adult male meadow voles captured in central Pennsylvania throughout the summer and exposed to various photoperiods also showed a similar

FIGURE 5

Number, area, and density of GnRH-ir neurons in hypothalamic regions of adult male deer mice (*Peromyscus maniculatus*). Bars indicate animals that did (SD-R, white) and did not (SD-NR, gray) undergo testicular regression after 8 weeks in short days (8L:16D), and animals that were housed in long days (16L:8D, LD, black bars) for 8 weeks. * represents measures on which SD-NR mice resembled SD-R mice; † represents measures on which SD-NR mice resembled LD mice; # represents measures on which SD-NR mice exhibited a unique GnRH-ir phenotype. (Data from Korytko et al. 1995.)

continuum of variance in reproductive response to photoperiod (Kerbeshian et al. 1994).

Meadow voles have been important models in studies of prenatal photoperiodic history on future reproductive responsiveness to daylength. For example, meadow vole dams with a photoperiod history of chronic short-day exposure (>20 consecutive weeks) give birth to offspring that only partially respond to the inhibitory effects of short days postnatally (i.e., testis weights are suppressed by short days, but spermatogenesis is not fully inhibited; Lee and Zucker 1988). In nature, such a maternal photoperiodic history would only be transmitted to pups born in the short days of late winter/early spring. From an ecological perspective, maternally induced nonresponsiveness may prepare pups for early spring breeding by permitting reproductive development in offspring born into these otherwise inhibitory short days (Lee and Zucker 1988).

Additionally, increased levels of activity inhibit responsiveness to short days in meadow voles. Male voles housed in short days with access to running wheels maintained fully developed testes, whereas voles without running wheel access exhibited gonadal collapse (Kerbeshian and Bronson 1996). The mechanisms by which wheel-running activity inhibits gonadal regression remain unspecified. The stimulatory effects of running wheel access persist under conditions of constant darkness and do not alter pineal melatonin rhythms, suggesting that exercise-induced disinhibition of reproductive physiology occurs via a post-pineal mechanism (Kerbeshian and Bronson 1996).

Syrian (Golden) Hamsters (*Mesocricetus auratus*)

Syrian (golden) hamsters (*Mesocricetus auratus*) inhabit a relatively narrow geographical region in northwest Syria (Clark 1987). Essentially solitary animals, Syrian hamsters live alone in extensive burrow systems (Walker 1975). The present domesticated strains of Syrian hamster have been developed from a single female and her 12 young trapped in Syria (Murphy 1985). Little is known about Syrian hamster reproduction in the wild; however, in the laboratory, hamsters are markedly photoperiodic breeders: photoperiods providing ≤12 hours of light per day completely inhibit gonadal development, whereas longer daylengths sustain gonadal function (Elliott 1976). Short-day nonresponders exist in laboratory stocks, but are infrequently reported in studies of photoperiodism (Eskes and Zucker 1978; Champney et al. 1997).

Intrinsic Determinants. A change in phase-relations between component circadian oscillators, resulting in an expansion of the duration of nocturnal melatonin secretion (α), is required for reproductive regression in response to short-day photoperiods. Naturally occurring variance in circadian τ can influence the pattern of entrainment to short days; hamsters with very long or short circadian periods are less likely to entrain to short days with decompressed α and gonadal regression (Eskes and Zucker 1978). No effort has been made to artificially select specifically for reproductive nonresponsiveness to short days in Syrian hamsters; however, individuals with a genetic mutation that renders the circadian τ abnormally short ($\tau = 20$–22 h; "tau-mutants") have been identified (Ralph and Menaker 1988), and these hamsters uniformly fail to undergo gonadal regression when exposed to short days (Menaker and Refinetti 1993). Thus, indirect evidence supports a role for intrinsic, genetically based factors in the expression of the nonresponder phenotype in this species. Prolonged exposure to continuous darkness permits expansion of α and nocturnal melatonin secretion (Freeman and Goldman 1997a); tau-mutants undergo gonadal regression when housed in constant darkness and when treated with exogenous melatonin, indicating a pre-pineal basis for nonresponsiveness in this strain (Stirland et al. 1995, 1996; Loudon et al. 1998).

Extrinsic Determinants. Both exercise and social interactions influence reproductive responsiveness to short days in the Syrian hamster (see below).

Neuroendocrine Mechanisms. Exercise attenuates responsiveness to short days in Syrian hamsters. Wheel running inhibits gonadal regression in response to melatonin treatments, and reverses photoperiod-induced anestrus (Borer et al. 1983; Pieper et al. 1988a). Wheel-running activity likely stimulates reproductive physiology at a post-pineal level, as exercise reverses the inhibitory effects of exogenous melatonin treatments (Pieper et al. 1988b).

Wheel-running activity directly stimulates go-nadotrophin secretion, indicating that nonre-sponsiveness in this paradigm may be an effect of positive masking at the level of the hypothal-amus or pituitary (Pieper et al. 1995).

Social interactions also attenuate responsive-ness to short days in Syrian hamsters. Three suc-cessive weeks of social interactions with females or female olfactory cues induced behavioral and physiological reproductive development in short-day, regressed male Syrian hamsters (Honrado and Fleming 1996). The neuro-endocrine level at which this reproductive dis-inhibition occurs has not been assessed.

ADAPTIVE FUNCTION OF PHOTOPERIOD NONRESPONSIVENESS

Nonresponders spend the unfavorable phase of the annual geophysical cycle (usually the winter) in a reproductively competent state. Assuming nonresponsiveness is maintained in a reproductive strategy set of a species because of its adaptive consequences, then periodic en-hanced fitness (relative to short-day responsive animals) must be associated with this nonsea-sonal approach to reproduction. If phenotypes on the responsive-nonresponsive continuum are subject to selection based on their fitness consequences, one ought to be able to assess the adaptive function of nonresponsiveness by asking several questions about the variation in reproductive strategies (Seger and Stubble-field 1996): (1) What is the function of nonre-sponsiveness? (2) How does variance in repro-ductive responsiveness to photoperiod affect individual fitness? (3) What are the immediate and long-term benefits associated with differ-ent levels of reproductive responsiveness? (4) What are the costs associated with adopting dif-ferent degrees of responsiveness?; and (5) Do any such costs change under variable environ-mental circumstances? Answers to these ques-tions are found in a combination of reasonable speculation and limited physiological data.

The modal seasonally breeding rodent en-gages in episodic reproduction, thus the most likely *function* of reproductive nonresponsive-ness is to permit an individual to ignore envi-ronmental cues that would otherwise tempo-rarily inhibit reproduction and thereby extend the current reproductively active phase. That the nonresponsive phenotype persists in wild

rodent populations suggests that there may be fitness benefits associated with the phenotype. But any selective advantages associated with nonresponsiveness are likely to be conditional, as the modal phenotype remains the one re-sponsive to photoperiod. Metabolic costs asso-ciated with the nonresponder phenotype have been reported (see below), but estimates of direct fitness associated with nonresponsive-ness, and quantitative associations between photoperiod nonresponsiveness and lifetime reproductive success, have yet to be described. Thus most of the above questions remain largely open, and the adaptive function of re-productive nonresponsiveness to photoperiod continues to be a matter of speculation. Exten-sive field studies are necessary to document nonresponsiveness in the wild, to ascertain whether and under what circumstances indi-vidual nonresponders breed, and to quantify the reproductive success enjoyed by nonre-sponders relative to that of sympatric photore-sponsive conspecifics. In the absence of such data, we remain ignorant as to the *function* of nonresponsiveness for a given species. In Sibe-rian hamsters, for example, there exists evi-dence to suggest that nonresponsiveness is an adaptive phenotype that has been maintained in the strategy set because of its fitness payoffs under conditional (albeit infrequent) circum-stances, and there also exists evidence that the phenotype is an entirely nonadaptive by-prod-uct of a circadian system which, for purposes of entrainment and phase shifting, requires coupling mechanisms that indirectly induce changes in τ and α.

COSTS OF NONRESPONSIVENESS
Metabolic Costs

Winter breeding provides a useful model for assessing the adaptiveness of a phenotypic character, in this case reproductive respon-siveness to photoperiod. Descriptions of the metabolic costs associated with not expressing a trait ("alternate strategies," in this case, re-productive nonresponsiveness to daylength) have the potential to highlight the benefits as-sociated with expression of the trait. To this end, a handful of studies have assessed the energetic "costs" of photoperiod nonrespon-siveness in rodents.

Short-day responses of photoperiodic Sibe-

rian hamsters include several energy-saving adaptations such as decreases in body weight (Hoffmann 1982), fur molt (Duncan and Goldman 1984), and gonadal and accessory gland regression (Bartness and Goldman 1988). Hamsters also deposit less white adipose tissue in several regions of the body in short days (Bartness et al. 1989). Decreases in brown adipose tissue (BAT) weight also occur under winter conditions (short photoperiods and low ambient temperatures, T_as); at the same time, the metabolic capacity of BAT undergoes changes that facilitate its use as a source of heat for nonshivering thermogenesis (Klingenspor et al. 1989). Behavioral changes consequent to short-day exposure include a substantial decrease in food intake (Fine and Bartness 1996) and the onset of daily torpor (Ruf and Heldmaier 1992). Siberian hamsters, in common with other daily heterotherms, continue to forage throughout the winter; periodic bouts of torpor permit a reduction of daily energy expenditure by approximately 20% (Ruf and Heldmaier 1992). The constellation of changes that constitute the response to short days in Siberian hamsters collectively functions to increase the likelihood of individual survival until the next breeding season.

A few studies have assessed the energetic costs associated with failing to adopt short-day metabolic adjustments. Exposure to low temperatures (10°C) and short days suppressed burrowing and increased nest building activity in reproductively responsive Siberian hamsters, but nonresponder hamsters did not exhibit these thermoregulatory adaptations. It is unclear, however, if the absence of short-day thermoregulatory behaviors was associated with increased energetic costs (Puchalski et al. 1988).

Nonresponder prairie voles maintained at 22°C in short days did not differ from responders with respect to food intake, basal metabolic rate, capacity for nonshivering thermogenesis, or amount of nesting material used. Thus, "energetic" traits did not follow the reproductive response to photoperiod (Moffatt et al. 1993). A similar pattern of results was observed in deer mice, except nonresponder deer mice exhibited a long-day pattern of nest building (Moffatt et al. 1993). Maintenance of long-day reproductive function and short-day metabolic adaptations are not mutually exclusive states.

The appearance of short-day traits in reproductive nonresponders suggests that these traits may be regulated by photoperiodic signals other than melatonin, or if such traits are indeed regulated by melatonin, indicates that melatonin signal transduction pathways disabled in the reproductive axis of nonresponders are functional in other physiological regulatory systems.

When nonresponders are exposed to more challenging environmental conditions, energetic costs associated with reproductive nonresponsiveness become apparent. Nonresponder deer mice exposed to low temperatures (5°C) and short days did not undergo decreases in body weight, an adaptation that normally lowers the total costs of thermoregulation (Heldmaier and Steinlechner 1981; Dark and Zucker 1985). Nonresponder deer mice ate more food under simulated winter conditions. Unlike voles, nonresponder deer mice evidently failed to develop a short-day behavioral-energetic phenotype. This is energetically costly: in short days at 5°C, daily energy requirements were reduced by 13% in photoresponsive males, as compared to an increase of 8% in nonresponsive animals (Figure 6; Ruf et al. 1997). Indeed, when energy balance is challenged by simulated winter conditions, the incidence of nonresponsiveness declines. Low temperatures with or without food restriction increase reproductive responsiveness to short days in hamsters (Larkin et al. 2001) and voles (Kriegsfeld et al. 2000a,b).

An adequate consideration of the adaptive significance of nonresponsiveness should include the energetic costs of winter breeding, along with the reproductive success associated with breeding when conspecifics are not. Little is known regarding the costs of nonresponsiveness and winter breeding in female rodents, as investigations to date have specified the energetic costs associated with nonresponsiveness only in males. The total costs of the reproductive effort should be equal in both sexes (Fisher 1930); however, this balance may involve changes in the relative costs of breeding at different times of the year (i.e., the costs of breeding may be exacerbated in one sex during winter breeding and in the other sex during summer breeding). For example, energetic costs are undoubtedly magnified when
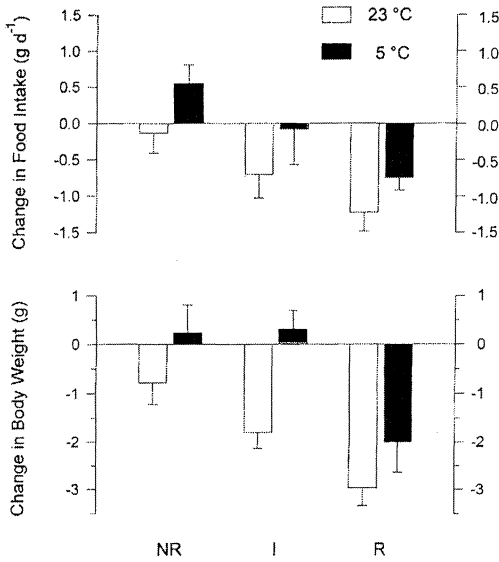
FIGURE 6

Short-day induced changes in food intake and body weight in deer mice *(Peromyscus maniculatus)* that exhibited complete (R), intermediate (I), or no gonadal regression (NR) after 8 weeks of exposure to a short-day photoperiod (8L:16D) and housed in ambient temperatures of 23°C or 5°C. (Data from Ruf et al. 1997.)

pregnancy and lactation occur at lower ambient temperatures. Whether, and from what sources, the myriad costs of reproduction are comparably increased in male rodents breeding out-of-season is unknown. Importantly, some costs associated with nonresponsiveness appear to be conditional, realized only under energetically challenging conditions. Nonresponsiveness represents a trade-off between reproduction and somatic maintenance at the expense of metabolic efficiency and positive energy balance. Yet to be described are the energetic costs associated with mounting host defense (immune) responses in responsive and nonresponsive rodents. Imperative are experiments that assess the actual fitness differences (e.g., lifetime reproductive success) between animals that are transiently reproductively quiescent versus those that attempt to breed year-round in the same environment.

Behavioral Costs

The advantages of maintaining reproductive function in winter may also interact with social organization to exact energetic costs. In-

dividuals of many rodent species shift from a highly territorial asocial strategy during the breeding season to a social, and highly interactive, existence during the winter. The seasonal change in social organization confers several advantages. During the breeding season, rodents control resources that promote their own survival and that of their offspring, and they often aggressively exclude their conspecifics from access to those resources. During the winter, however, this strategy is abandoned in favor of group-living, which conserves energy and enhances survival in the face of low temperatures and reduced food availability. Many species of rodents conserve energy during the winter by forming aggregations of huddling animals (West and Dublin 1984). In these aggregations, different sexes and even different species are commingled (Madison et al. 1984). During the winter months, for example, meadow voles move into the spruce forest habitats occupied by the red-backed voles, presumably to take advantage of the protective cover provided by the trees. In some cases, they share nests with other rodent species (Madison et al. 1984). Individual meadow voles trapped during the winter and tested in paired encounters exhibited less interspecific aggression than summer-trapped voles (Turner et al. 1975). The winter reduction in aggressiveness permits energy-saving habitat sharing.

A potential cost of nonresponsiveness may be that reproductively competent males, because of unusual aggressiveness during the winter, are unable to benefit from communal huddling and thus incur greater energetic costs in overwintering. This contention is supported by a field study of winter nesting behavior of prairie voles (McShea 1990). Most voles in the population studied were reproductively inactive during the winter and formed groups of huddling individuals. Two males, however, remained in breeding condition and were never observed to huddle with other animals. In pair-wise tests of aggression, these two males were much more aggressive than reproductively quiescent individuals. In another study, reproductive status also influenced odor preferences of meadow voles maintained in simulated winter daylengths (Ferkin and Gorman 1992). Males that retained reproductive capability in winter daylengths preferred the odors

of females that also failed to inhibit reproduction during short days. This preference may facilitate the sporadic occurrences of winter breeding frequently reported for this species (reviewed in Nelson 1987).

HYPOTHESES FOR MAINTENANCE

Several hypotheses may explain why, from an ultimate perspective, individuals within wild populations of several rodent species fail to undergo reproductive regression and instead attempt to breed throughout the late summer, autumn, and winter.

Balanced Polyphenism Hypothesis (Nelson 1987)

For individual small rodents, a single reproductive failure may have disastrous consequences. Production of offspring that vary in their reproductive responsiveness to photoperiod may increase fitness. For example, an animal that relies exclusively on photoperiod to time its breeding may reproduce at inappropriate times because of unseasonable weather (e.g., a late snow pack), whereas a sibling that does not become reproductively competent until adequate nutrition is available is buffered from these events. The inclusive fitness of the parents and the unsuccessful (obligately photoperiodic) sibling is enhanced by this phenotypic variation. Because each of these traits can be advantageous under certain circumstances, each phenotype can be maintained in a population at a stable frequency and form a balanced polyphenism. A balanced polyphenism may exist between opportunistic individuals that ignore photoperiod information, rely on more proximate cues, and thus are capable of winter breeding, and the more conservative obligate reproductive strategists. Data from studies of deer mice suggest that a balanced polyphenism exists among male deer mice responsive to photoperiod, temperature, and food and water availability (Desjardins and Lopez 1983; Blank and Desjardins 1985); apparently one mother can produce all four phenotypes in a single litter.

Nonadaptive Hypothesis

In contrast to the Balanced Polyphenism Hypothesis, this hypothesis suggests that, in some species, photoperiod nonresponsiveness is a nonadaptive consequence of mechanisms necessary to maintain a normally functioning circadian pacemaker. In the case of the Siberian hamster, this hypothesis contends that oscillator coupling mechanisms, which permit entrainment of the circadian system to seasonal changes in the light-dark cycle, inadvertently cause circadian oscillators to get "stuck" in a long-day entrainment pattern if animals are exposed to specific environmental conditions (an environmental "trigger," e.g., 18L), rendering the animals permanently unresponsive to short days thereafter. Such a mechanism could be maintained by antagonistic pleiotropy: if the fitness benefits of a seasonally adjustable circadian clock were sufficiently high, such mechanisms could be maintained despite their occasional induction of nonresponsiveness. According to this hypothesis, periodic successful winter breeding plays no role in the maintenance of the trait in a population. This hypothesis requires that, for nonresponsiveness genes to be maintained at some stable equilibrium: (1) their short-term consequences not be fatal, and (2) the environmental trigger occur after animals have successfully reproduced. Extrapolating Gorman and Zucker's (1997) data to a naturalistic context, Siberian hamsters that have experienced photoperiods sufficiently long enough to induce nonresponsiveness must have lived through the summer solstice, and therefore were likely adults participating in the previous mating season. Given the low probability of successful overwintering in this short-lived species, their residual reproductive value may be negligible. Short-day responsiveness thus may be a selectively neutral trait in these aged, reproductively successful individuals.

It is important to note that the circadian problems that mediate nonresponsiveness in laboratory strains of Siberian hamster have not been observed in nonresponders of outbred photoperiodic rodent species. Although properties of the circadian system of nonresponder white-footed mice differ from those of responders, these differences do not appear to play a causal role in the mediation of nonresponsiveness (Majoy and Heideman 2000). It is currently unknown whether the induction of nonresponsiveness by very long photoperiods is a ubiquitous phenomenon or one restricted to Siberian hamsters. Comparative stud-

ies are required to ascertain whether photic triggering of nonresponsiveness is a common mechanism that permits short-lived rodents to capitalize on mild winters.

Immunocompetence Hypothesis

This hypothesis suggests that in a given photoperiodic population, reproductive nonresponders are a subset comprised of individuals that have an immunological advantage that predisposes them to be more capable of successfully overwintering (Nelson et al. 1996). Energetic resources allocated to reproduction likely represent a substantial proportion of a nonresponder's winter energy budget. Given a finite energy budget, maintenance of reproductive competence during the winter requires diverting energetic reserves away from host defense. If some individuals were immunologically superior, and thus could better endure reduced investment in immune function during the winter, the fitness costs (in terms of risk of infection, colonization, and death) associated with nonresponsiveness in their case might be sufficiently low to skew the selective equation in favor of attempting to breed during the winter. Unlike the Nonadaptive Byproduct Hypothesis, this hypothesis requires periodic successful winter breeding to maintain nonresponsiveness genes in the reproductive strategy set. A testable prediction based on this hypothesis would be that, relative to responsive animals, animals from nonresponder lineages would have higher baseline immune function under winter conditions and/or would require less energy to mount an immune response to an antigen/pathogen under appropriate winter conditions.

SUMMARY AND PROSPECTUS

Daylength per se confers no fitness benefits, but it serves as a relatively noise-free proximate cue that is highly predictive of seasonal changes in biotic (food, water, nest materials) and abiotic (temperature) factors essential to reproduction (Farner 1985; Goldman and Nelson 1993). Photoperiodic regulation of reproduction is thus an adaptive approach to the challenges of a seasonally changing environment. Populations of photoperiodic rodents contain a substantial proportion of individuals that do not adopt a photoperiodic breeding strategy and are unresponsive to inhibitory daylength cues. Presumably, in nature these individuals mate and attempt to rear young during the energetically unfavorable winter months. The mechanisms by which the reproductive neuroendocrine system fails to respond to short-day signals vary substantially between rodent species. A loss of gonadotrophic responsiveness to inhibitory patterns of pineal melatonin secretion is associated with reproductive nonresponsiveness in outbred populations of voles, deer mice, and white-footed mice, whereas pre-pineal (circadian) abnormalities appear to mediate nonresponsiveness in Siberian hamsters. Whether circadian mediation of nonresponsiveness represents a field phenomenon or an artifact of domestication is presently unknown.

Although animals that breed continuously should have higher direct fitness than those that only breed seasonally, individuals whose offspring do not survive to maturity will achieve no reproductive success and may even lose residual reproductive value (Clutton-Brock 1991). Advanced age has been theoretically and empirically associated with nonresponsiveness—animals unlikely to successfully overwinter risk little by attempting to breed against an energetically unfavorable landscape. The proximate costs of photoperiod nonresponsiveness and winter breeding in small-bodied rodents has yet to receive full attention. Costs associated with nonresponsiveness have been described for male rodents, but the ability of females to gestate and nurse a litter during the winter months may dictate whether reproductive success is realized through winter breeding.

Noteworthy is the relative absence of counterparts to photoperiod nonresponders in species whose seasonal reproductive transitions are regulated by a circannual clock (Type II species). If verified with field data, an absence of polyphenisms in reproductive seasonality in these species would suggest that such circannual mechanisms only evolve when the advantages of seasonality are so great as to preclude any significant degree of success by individuals that violate the rule, or conversely, that photoperiodic (Type I) mechanisms tend to evolve when alternative (nonphotoperiodic, facultative) reproductive strategies periodically succeed (B Goldman, personal communication).

Indeed, the substantial proportion of photoperiod nonresponders in most rodent populations challenges the notion of photoperiodism as an adaptive response to a temporally variable environment. The relatively high incidence of overwinter mortality should select against genes that code for seasonal reproductive quiescence. Thus, substantial reproductive success must be realized by individuals that survive overwinter to breed during the energetically favorable spring months, as well as by the infrequent individual that manages to breed throughout the winter. The incidence of nonresponsiveness in any population likely reflects a product of stabilizing selection driven by the severity of recent winter conditions.

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