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Photoperiodic Control of Seasonal Body Weight Cycles in Hamsters[1]

TIMOTHY J. BARTNESS* AND GEORGE N. WADE

*Worcester Foundation for Experimental Biology, 222 Maple Avenue, Shrewsbury, MA 01545
and Division of Neuroscience and Behavior, Department of Psychology
University of Massachusetts, Amherst, MA 01003

BARTNESS, T. J. AND G. N. WADE. *Photoperiodic control of seasonal body weight cycles in hamsters.* NEUROSCI BIOBEHAV REV 9(4) 599–612, 1985.—Syrian *(Mesocricetus auratus)* and Siberian *(Phodopus sungorus sungorus)* hamsters exhibit seasonal changes in body weight mainly by altering their carcass lipid stores. These seasonal changes are triggered largely by the photoperiod. Although both species exhibit gonadal regression when exposed to short photoperiods ("winterlike" daylength), they show opposite body weight changes. Syrian hamsters gain weight, but Siberian hamsters lose weight following short photoperiod exposure. Syrian hamsters prepare for overwintering by increasing energy stored as carcass lipid. In contrast, Siberian hamsters decrease their metabolic mass and therefore require lower energy intake for energy maintenance. In Syrian, and perhaps Siberian hamsters the short day-induced weight changes are exaggerated by high fat diets. Both species show photoperiod-induced changes in body weight without changing their food intake, suggesting a metabolic basis for these effects. In Syrian hamsters, the obesity is not secondary to gonadal regression, whereas in Siberian hamsters, the decrease in body weight is independent of the gonads for males but may be dependent upon the gonads in females. The pineal gland and its hormone, melatonin, are important transducers of photoperiodic signals in hamsters. This is certainly true for Siberian hamsters, in which pinealectomy blocks the short day-induced body weight loss. In contrast, pinealectomy has little effect on short day-induced weight gain in Syrian hamsters. Nevertheless, in both species, the body weight and gonadal changes induced by short day exposure are mimicked by systemic administration of melatonin in long day-housed animals. Thus, for these two hamster species, the same hormone, melatonin, produces opposite effects on body weight but does so by affecting the same carcass component. The target sites of action for the effects of melatonin on body weight change, energy metabolism, and reproductive status are not known. However, the suprachiasmatic and paraventricular nuclei of the hypothalamus are potentially important sites of action. The target site(s) and mechanism(s) of action for the pineal/melatonin-independent effect of photoperiod on body weight in Syrian hamsters are also unknown. This photoperiodic response is highly unusual among mammals in that it is not pineal-dependent. Studies of the mechanisms underlying these body weight changes in Syrian and Siberian hamsters may provide fundamental knowledge about how environmental influences affect obesity and they may also provide insight into the various strategies for overwintering shaped by natural selection. Further contributions in both fields of study may be made by comparative studies of Syrian and Siberian hamsters which gain and lose body weight, respectively, and Turkish hamsters which show no changes in body weight when exposed to short days.

Hamsters   Body weight   Body fat   Pineal   Melatonin   Photoperiod   Annual cycles

IN small mammals, as well as in human beings, body weight is affected by a multiplicity of factors. A number of small mammals show dramatic seasonal changes in body weight, reflected in large part as changes in body fat. For example, sciurid rodents such as ground squirrels, marmots and woodchucks show increased body weight, mostly as carcass lipid, during an autumn pre-winter fattening phase [28, 84, 85, 88]. These animals hibernate in the winter during which time body weight decreases as the prehibernatory lipid stores are gradually depleted [84]. This cycle of weight gain and loss across the seasons represents an example of a circannual rhythm. That is, even in the absence of any change in the environment such as temperature or daylength, the body weight cycle persists [28, 54, 88, 133–135]. The under-

lying timekeeping mechanism remains unknown [22, 23, 27, 132–134].

A number of muroid rodents such as hamsters and voles also show seasonal changes in body weight [1–3, 14, 24–26, 38, 59–62, 22, 104, 120–125, 155] once again primarily, although not exclusively, as body fat [1–3, 25, 55, 115–118]. These species are distinctly different from sciurid rodents, in that the changes in body weight are triggered by environmental cues such as photoperiod (and perhaps diet) and have no known underlying circannual rhythm. The change in daylength is the principal cue as to the time of year for these species. It is the photoperiodic regulation of body weight, body fat, food intake and energy metabolism of hamsters, especially in Syrian or golden hamsters *(Mesocricetus au-*

ratus) and Siberian or Djungarian hamsters *(Phodopus sungorus sungorus)* that is the focus of this review. Photoperiodic regulation of these factors in voles has been reviewed recently [27].

CIRCADIAN RHYTHMS AND PHOTOPERIODISM

It is behond the scope of this review to discuss biological rhythms in great detail, but the interested reader is referred to some recent reviews in the area of chronobiology (i.e., biological time-keeping) [5, 33, 83]. In muroid rodents the determination of daylength, and therefore the season, is through circadian rhythms. Circadian rhythms have a period of about 24 hours and persist in the absence of environmental cues such as photoperiod and temperature changes. The current view of how circadian rhythms participate in the photoperiodic control of seasonal biological rhythms was formulated by Bunning for daylength measurement in plants [13]. Bunning suggested that the photostimulatory or nonphotostimulatory effect of a given photoperiod was dependent upon the temporal relationship between the photoperiod light and a circadian rhythm of photoperiodic photoresponsivity (CRPP). Elliott [32] tested and confirmed this CRPP model for the regulation of testis function in a series of elegantly designed experiments in Syrian hamsters. When light occurred during the responsive part of the CRPP, the photoschedule was interpreted as long days and testis function was maintained. However, if light fell only on the nonresponsive part of this rhythm, the photoschedule was interpreted as a short day and testicular regression occurred. Thus, in Syrian hamsters the duration of light is unimportant for daylength determination, but rather the timing of the light presentation with respect to the "endogenous 24 hour clock" [32].

THE PINEAL GLAND, MELATONIN AND PHOTOPERIODIC CONTROL OF REPRODUCTIVE CYCLES IN HAMSTERS

Syrian and Siberian hamsters are long-day breeders. In contrast to other photoperiodic animals such as sheep and deer, sexual behavior, gestation, lactation and weaning occur across the spring and summer months when the daylength is increasing or long (for review see [5]). The minimal daylength to stimulate testis growth is 12.5 hours in Syrian [40] and 13.0 hours in Siberian hamsters [65]. Hamsters kept in photoperiods greater than these critical values will remain reproductively competent. However, with prolonged exposure to photoperiods less than these critical daylengths or to naturally-decreasing photoperiods, there is a collapse of the reproductive system. After about four to five months Syrian or Siberian hamsters maintained in short photoperiods exhibit a spontaneous recrudescence of the gonads [59, 91, 114]. The adaptive significance of spontaneous recrudescence may be that gonadal function and hence reproductive competence will be achieved slightly before the critical daylength occurs in the spring, thus enabling these animals to begin the reproductive cycle without delay as favorable weather approaches [92].

How is the daylength cue translated into neuroendocrine changes that govern gonadal status and other seasonal responses? The key element in these changes is the pineal gland and its hormone, melatonin (for review see [33, 43, 63, 64, 93]). The synthesis of pineal melatonin is controlled by light. The neural transmission of this signal is through a circuitous route from the retina to the pineal gland. Light stimulates the retina which in turn sends this information to a
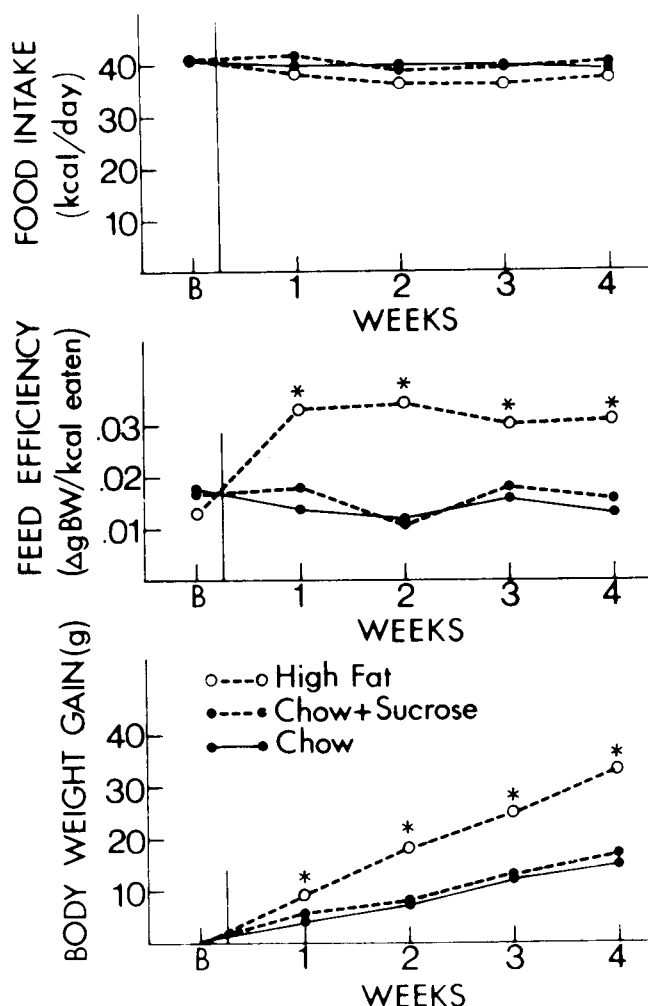

FIG. 1. Food intake, body weight gain and feed efficiency (g body weight gain per kcal eaten) of male Syrian hamsters given access to a high-fat diet, chow plus a 32% sucrose solution or chow only. Asterisks indicate $p<0.01$ versus chow-fed groups (Reprinted with permission from Pergamon Press, Ltd [119]).

number of neural structures, most importantly to the suprachiasmatic nuclei (SCN). The SCN send efferents to the paraventricular nuclei (PVN) of the hypothalamus [82,106]. The PVN, in turn, send axons to the intermediolateral horn of the spinal cord which contains cell bodies of the sympathetic nervous system [98,107]. These cells project to neurons in the superior cervical ganglia, where postsynaptic neurons send projections directly to the pinealocytes via the nervi conarri [70]. During the night, serotonin is converted to melatonin in the pineal through the action of the enzymes, N-acetyltransferase and hydroxyindole-O-methyltransferase [79]. Decreased release of the gonadotrophins LH, FSH, and prolactin are associated with short photoperiod-induced gonadal regression in both Syrian and Siberian hamsters. These decreases are thought to be mediated by melatonin [11, 31, 44, 109, 130].

In Siberian hamsters, and perhaps in Syrian hamsters, short photoperiods (thus, long nights) produce an increase in the *duration* of nocturnal melatonin secretion resulting in the collapse of the reproductive system [17,34]. Therefore, the

daily duration of pineal melatonin secretion serves as the signal for the seasonal timekeeper of these hamsters. As would be predicted, pinealectomy blocks short day-induced gonadal regression in both species [56,60]. Further support for the role of melatonin in short day-induced regression are the findings that timed, systemic injections of melatonin in long day-housed Syrian and Siberian hamsters (~3 hr prior to lights-out) also result in gonadal regression. This injection schedule is thought to mimic the effects of short days on the reproductive system in hamsters by coupling the exogenously administered melatonin with the naturally-occurring nocturnal release of melatonin. This lengthened period of melatonin stimulation is interpreted by these long photoperiod-housed hamsters as a short day [1, 2, 31, 110, 111, 123, 124, 130].

DIETARY OBESITY IN HAMSTERS

Our initial interest in the short photoperiod-induced obesity in Syrian hamsters was prompted by our finding that hamsters fed a high-fat diet become obese without a concurrent increase in caloric intake [119] (Fig. 1). This obesity without overeating is in sharp contrast to that of rats and mice which also become obese when fed lipid-rich diets but typically show a marked increase in caloric intake ([10, 21, 75, 99, but cf. [81]). The cause of the high-fat diet-induced obesity in Syrian hamsters is a decrease in energy expenditure. We found that fat-fed hamsters have a reduced resting metabolic rate, as indicated by whole-animal oxygen consumption, relative to their chow-fed counterparts [121].

Paradoxically, this diet-induced reduction in energy expenditure is accompanied by an impressive growth in brown adipose tissue [119], an important energy-*expending* organ [39,96]. Brown adipose tissue is also a major site of nonshivering thermogenesis [39], and thermogenic capacity (norepinephrine-stimulated oxygen consumption) is significantly enhanced in fat-fed hamsters [119]. The causes of this diet-induced brown adipose tissue growth are unclear, although it is evident that they do not include increased sympathetic activity as is found in rats [101]. In contrast, fat-fed Syrian hamsters exhibit a decrease in norepinephrine content and turnover in their brown adipose tissue [48].

The phenomenon of high fat diet-induced obesity is robust, occurring not only with a vegetable shortening-based diet [1, 3, 119–123] but also with corn oil (long chained, polyunsaturated vegetable fat) and with a medium chained triglyceride diet [121]. Recently, using a diet of mixed snack foods, the so-called "cafeteria diet" (38% fat), Syrian hamsters also become obese but with an associated hyperphagia [100]. Using a more naturalistic diet, obesity without overeating has also been reported in Syrian hamsters fed sunflower seeds (61% fat) [112].

Of particular interest to this review is that high fat diet-induced obesity is exaggerated by short photoperiod exposure in Syrian hamsters [115] (Fig. 2). This finding prompted us to speculate that this obesity may have an adaptive significance in preparing hamsters for winter survival by increasing lipid stores at a time when external sources of energy may be limiting, by increasing thermal insulation, and by increasing thermogenic capacity via growth of brown adipose tissue. Since the behavioral ecology of these animals is virtually unknown, this was only speculation. However, in another species, Belding ground squirrels *(Spermophilus beldingi beldingi),* the mainstay of their diet is grasses in the summer and changes to seeds (a lipid-rich food source) in the
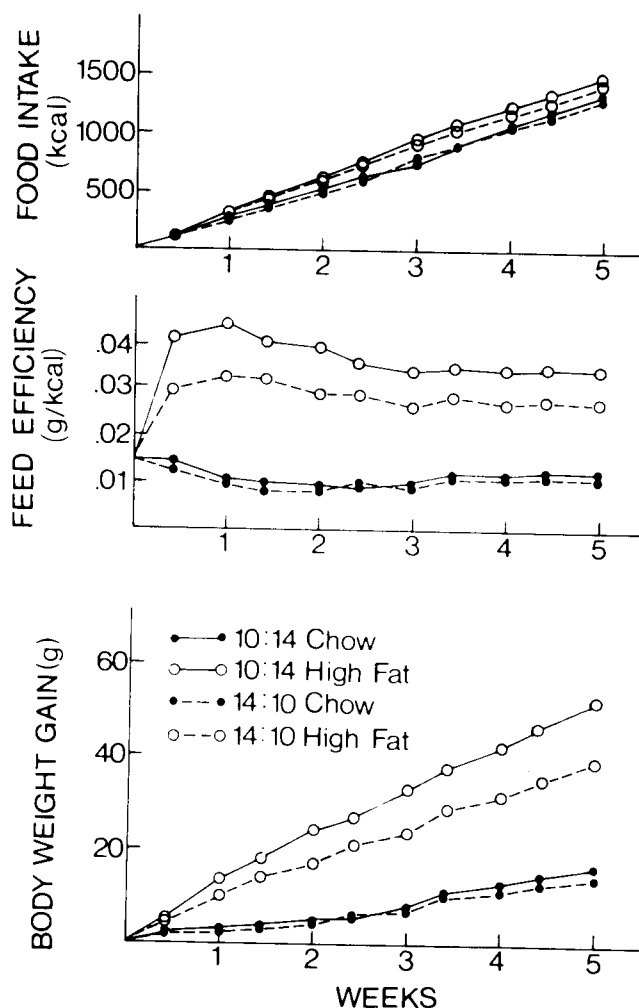

FIG. 2. Cumulative caloric intake, body weight gain, and feed efficiency of male Syrian hamsters housed in a 14:10 hour (long photoperiod) or a 10:14 hour (short photoperiod) light:dark cycle (LD) and fed Purina chow (No. 5001) or a high-fat diet (Reprinted with permission from Pergamon Press, Ltd [120]).

later summer and autumn during the fattening phase of their weight cycle [84]. Perhaps Syrian hamsters do likewise. They are certainly avid hoarders and consumers of seeds when they are available [7, 9, 72, 102, 112].

In contrast, Siberian hamsters do not gain weight or fatten when fed the vegetable shortening-based high fat diet [121]. On occasion they do overeat on lipid-rich diets, but when this occurs, an impressive diet-induced thermogenesis [77] prevents weight gains [77,121]. However, if maintained on only a sunflower seed diet Siberian hamsters will show small increases in lipid accretion (Gerhard Heldmaier, personal communication).

PHOTOPERIOD AND BODY WEIGHT CHANGE

Hamsters exposed to short ("winter-like") photoperiods exhibit a constellation of physiological changes that appear to be orchestrated by the pineal gland and its hormone, melatonin (the only exception to be discussed below). These changes include decreased gonadal function [11, 40, 59, 61]

and thyroid activity [116–118], pelage color change and increased hair density [29–31, 61], increased thermogenic capacity [49–53, 103], and the engagement in daily torpor [50, 51, 115] or hibernation [66]. Depending upon the hamster species, short photoperiod exposure can result in increased or decreased body weight, carcass lipid, and food intake [1–3, 14, 15, 51, 53, 58, 59, 62, 66, 77, 80, 81, 104, 115, 120, 123, 124].

SYRIAN HAMSTERS

Syrian hamsters *(Mesocricetus auratus)* exhibit their minimal body weight during long photoperiod exposure, coincident with a functional gonadal status [1, 3, 14, 57, 120–123]. Following exposure to short photoperiods, body weight increases (Fig. 3) and the gonads regress [1, 3, 14, 58, 120–123]. Recall that with prolonged exposure to short photoperiods the gonads spontaneously recrudesce [91,114]. We have also found that the short photoperiod-induced body weight increase "spontaneously" reverses following a similar time course (15 to 17 weeks) (Fig. 4) [123]. These photoperiod-induced increases and decreases in body weight are reflected primarily as carcass lipid [1, 3, 58, 120–123]. The short day-induced obesity is greater in female than male Syrian hamsters [1,120] and is exaggerated in hamsters fed a high fat-diet (Figs. 3 and 4) [1, 120–123]. Furthermore, these changes are seen without a concomitant increase in caloric intake. (Hamsters fed a high-fat diet will overeat on occasion [3, 48, 100, 128], but short photoperiod-induced weight gains are never accompanied by overeating.) Since the increased body weight is independent of food intake, these animals exhibit an increase in metabolic efficiency. How might this obesity without overeating be accomplished?

One obvious means by which energy might be saved would be to decrease energy expended as locomotor activity. The effect of photoperiod on home cage locomotor activity in hamsters has not been examined. However, locomotor activity, as measured by vertical running-wheel activity, has been studied. Short photoperiod-exposed Syrian hamsters decrease their activity levels relative to their long day controls [35, 36, 128]. However, how this decrease in wheel-running translates into energy expenditure as locomotor activity in the home cage is unknown and the critical missing information for this comparison. We feel a change in locomotor activity most likely contributes relatively little to the increased feed efficiency seen in short photoperiod-exposed hamsters housed singly in small rodent cages.

The increased metabolic efficiency exhibited by short photoperiod-exposed Syrian hamsters could be due to a reduced metabolic rate. Indeed, hamsters housed in short photoperiods or given afternoon melatonin injections have reduced circulating levels of thyroid hormones [116–118], a condition associated with decreased metabolic rates. However, we believe it unlikely that the short day-induced reduction in thyroid activity is solely responsible for the increased energy retention, because pinealectomy prevents the effect of short days on the thyroid [112] without preventing the body weight gains [1] (see below). Decreased thyroid activity probably contributes to, but is not essential for, the increased metabolic efficiency.

Prolactin may play a role in the growth of brown adipose tissue and the consequent increase in thermogenic capacity in hamsters exposed to short photoperiods. Short photoperiods cause a decrease in prolactin secretion [11, 44, 109] and a growth of brown adipose tissue [1, 55, 120–123]. Con-
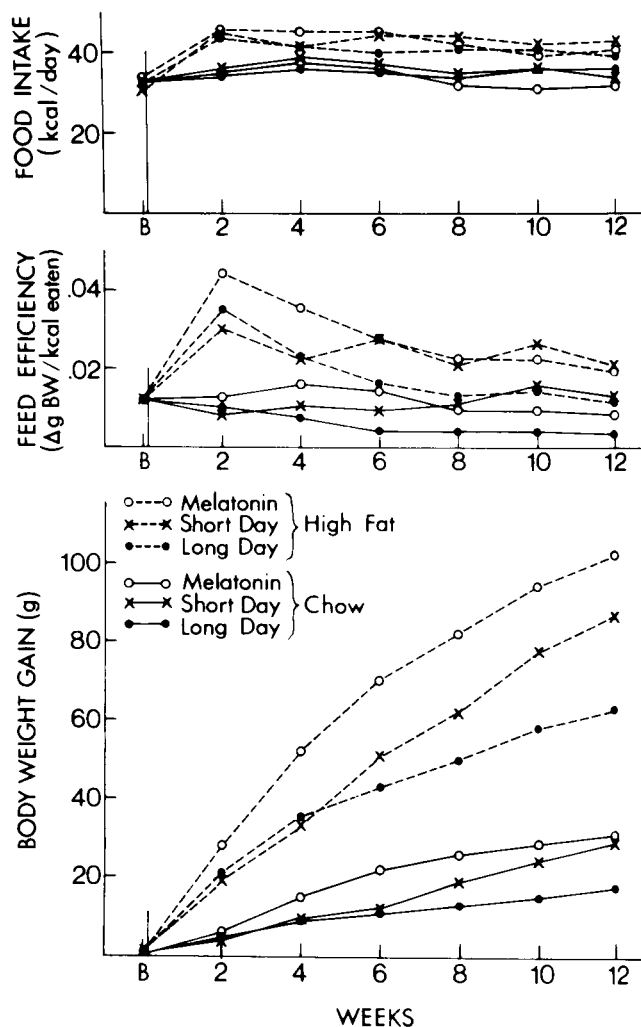

FIG. 3. Food intake, feed efficiency and body weight gain of female Syrian hamsters housed in a LD 16:8 (long day) or LD 8:16 (short day) photoperiod and fed either chow or a high-fat diet. Long photoperiod-housed hamsters received daily SC injections of melatonin (25 μg; 3 hours before lights-out) or the ethanolic saline vehicle (Reprinted with permission from The Endocrine Society [1]).

versely, brown adipose tissue mass and thermogenic activity are suppressed during pregnancy and lactation [127] when circulating prolactin levels are elevated in hamsters [4,11]. Thus, prolactin may suppress brown adipose tissue growth and thermogenic activity. However, prolactin levels covary with progesterone in these circumstances [11] and it may be the interplay among prolactin, progesterone and estradiol (the latter is decreased during pregnancy, lactation and short photoperiods in hamsters [129]) that promotes these changes in female Syrian hamsters. Finally, Borer [8] found that a 10-fold increase in serum prolactin produced by pituitary explants reduced carcass lipid in short day-exposed female Syrian hamsters. Whether this change in body weight was due to brown adipose tissue activation and an associated increase in energy expenditure is not known.

The increased body weight in Syrian hamsters housed in short photoperiods seem to be mediated, in part, by the pineal gland and melatonin. Pineal melatonin content [131]
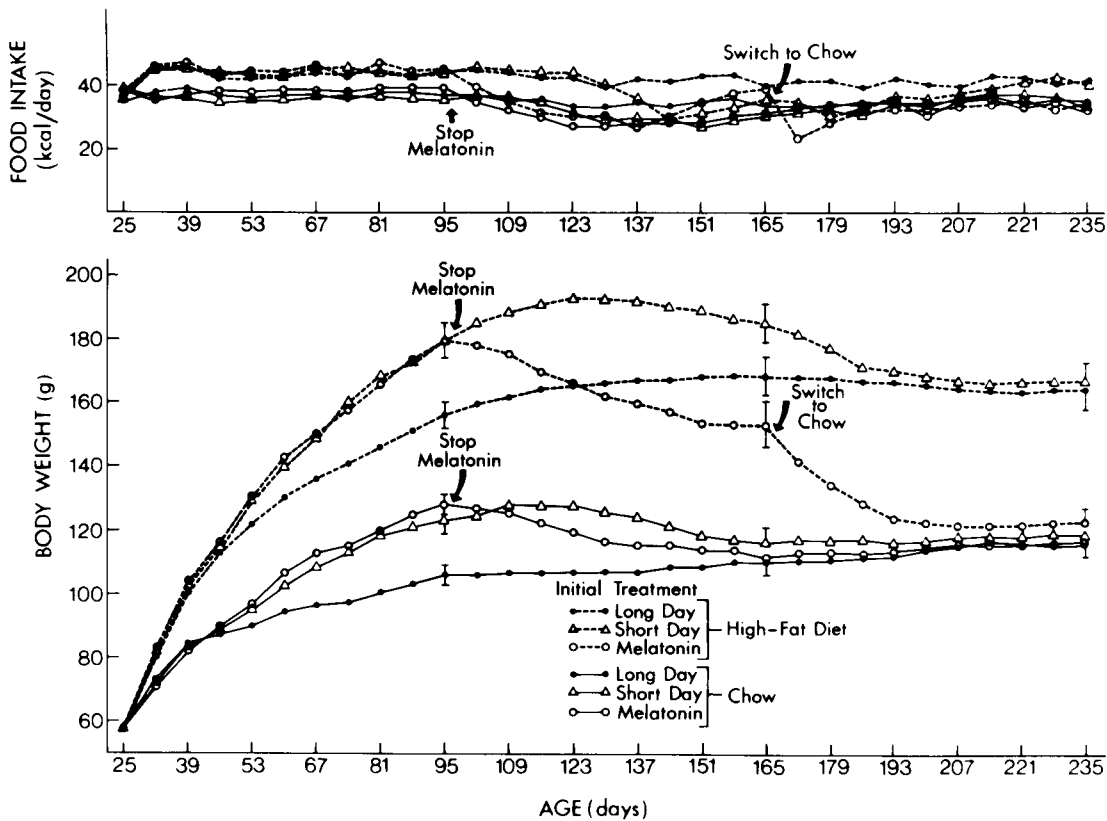
FIG. 4. Food intake and body weight of female Syrian hamsters fed chow or a high-fat diet starting at 25 days of age and housed in a LD 16:8 (long photoperiod) and given daily SC injections of melatonin (25 μg) or the saline vehicle for the first 10 weeks. Other animals were housed in a LD 8:16 (short photoperiod) throughout the experiment. One group was switched to the chow diet after 20 weeks of high-fat diet-feeding (Reprinted with permission from The American Physiological Society [122]).

and the duration of high circulating melatonin levels are increased in short photoperiods in Siberian hamsters [43], and perhaps also in Syrian hamsters [32]. Because afternoon, but not morning subcutaneous injections of melatonin in long photoperiod-housed Syrian or Siberian hamsters lead to regression of the gonads similar to that which occurs naturally in short photoperiods [31, 110, 111, 123, 130], we examined changes in body weight and energy metabolism in long photoperiod-housed Syrian hamsters given afternoon melatonin injections (25 μg melatonin 3 hours prior to lights-out). The short photoperiod-induced increases in body weight gain, feed efficiency, carcass lipid content, brown adipose tissue mass and thermogenic capacity were mimicked by afternoon [1,122], but not morning [122] melatonin injections in both adult male and female hamsters [1,122]. These effects were exaggerated in animals fed a high fat diet (Fig. 5). In addition, we examined the effects of lower doses of melatonin injected in the afternoon. Ten micrograms of melatonin were sufficient to increase body weight, adiposity and brown adipose tissue wet weights and to decrease uterine weight and suspend estrous cyclicity (Figs. 5 and 6). On the other hand, 2.5 μg of melatonin increased body weight and fat content but had no effect on brown adipose tissue weight or reproductive function [122]. The results suggest differential sensitivity in melatonin-sensitive endpoints and indicate that there may be independent effects of melatonin on reproduction and body weight.

There is some controversy concerning the reproductive responsiveness of prepubertal Syrian hamsters to melatonin or short photoperiods [94, 95, 133]. To determine whether energy balance would be affected at this age, 25 day-old female hamsters were treated with melatonin or placed in a short photoperiod. These weanling hamsters increased their body weight to both treatments with a latency comparable to that of adults [122]. Therefore, photoperiod affects body weight in prepubertal Syrian hamsters, but perhaps not reproductive status. This finding, coupled with our observation that weanling hamsters exhibit a rapid response to a high-fat diet, significantly increasing their body weight within one week [121], is consistent with our speculation that these responses may be of adaptive significance in promoting winter survival. Thus, the fat accretion induced by the interaction of the high-fat diet with short photoperiods would increase not only energy reserves as carcass lipid and the insulative property of subcutaneous fat but also promote morphological changes in brown adipose tissue that would increase its thermogenic capacity [121, 122, 124].

Because short photoperiod exposure or afternoon melatonin injections produce gonadal regression, it might be argued that the short photoperiod-induced changes in body weight and energy metabolism may have been the consequence of a functional gonadectomy. For example, ovariectomized Syrian hamsters increase their body weight, in large part as body fat (Slusser and Wade, unpublished observa-
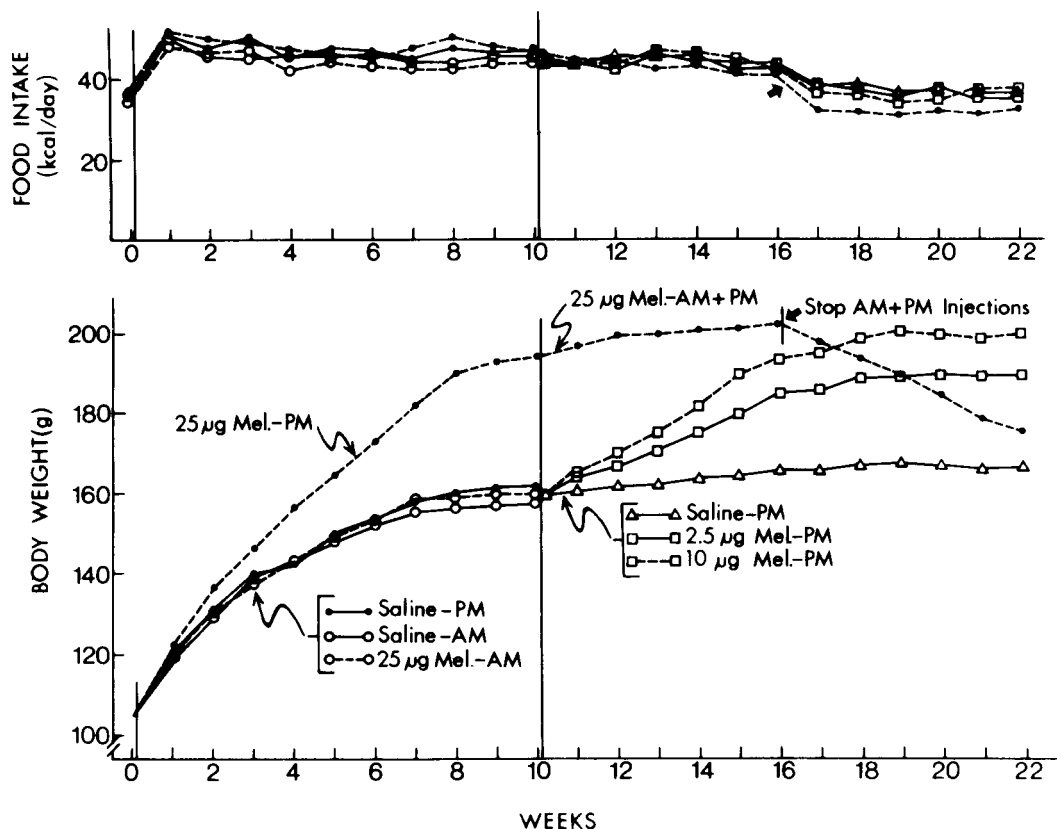
FIG. 5. Food intake and body weight of female Syrian hamsters fed a high-fat diet and given daily SC injections of melatonin (MEL) or the saline vehicle. Animals were housed in LD 16:8 (long photoperiod) and injections were given 3 hours before lights-out (p.m.) or at the midpoint of the light phase (a.m.). Treatments were changed at week 10 as indicated (Reprinted with permission from The American Physiological Society [122]).
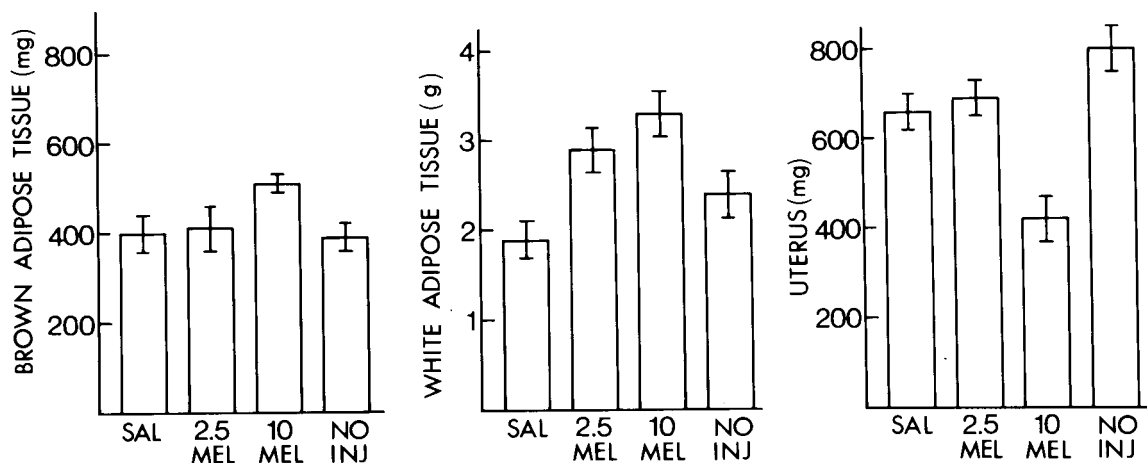

FIG. 6. Weights of interscapular brown adipose tissue, parametrial white adipose tissue, and uterus of Syrian hamsters fed a high-fat diet and given daily injections of melatonin (MEL, 2.5 or 10 μg) or saline (SAL) for 12 weeks. An additional group (NO INJ) had gone without melatonin injections for 6 weeks (cf. Fig. 5) (Reprinted with permission from The American Physiological Society [122]).

tions). The dependence of the short photoperiod-induced obesity on decreased gonadal steroid production was tested in ovariectomized Syrian hamsters whose body weights had stabilized. These animals were fed a high-fat diet and given afternoon melatonin or vehicle injections or were moved into a short photoperiod. The short photoperiod-induced increase

in body weight, adiposity, feed efficiency and brown adipose tissue mass were all observed in ovariectomized animals at levels comparable to that seen in gonadally-intact hamsters [1]. Thus, these effects of short photoperiods on energy balance are independent of the gonads, at least in female hamsters. It is likely that photoperiod-induced changes in gonadal function normally contribute to the changes in energy balance, even though they are not essential for the weight gains to occur.

Finally, because pinealectomy blocks the neuroendocrine responses mediating short photoperiod-induced gonadal regression and reduced thyroid function in Syrian hamsters, we tested the dependence of the short photoperiod-induced increases in body weight and energy metabolism on an intact pineal gland. It had been previously reported that pinealectomized, chow-fed male Syrian hamsters still exhibit an increase in body weight in short days, an effect blocked by blinding [58]. Since high fat diet-fed female hamsters show exaggerated body weight and energy-related responses to short photoperiods, we examined the effects of pinealectomy on these measures in fat-fed female hamsters housed in long or short days. Short photoperiod-housed, pinealectomized hamsters had increases in body weight, metabolic efficiency, and brown and white adipose tissue mass similar to that of pineal-intact hamsters. These animals were indeed pinealectomized as indicated by their continued estrous cyclicity and maintenance of uterine weights. Thus, in addition to any pineal/melatonin-mediated mechanisms, short photoperiods also affect energy metabolism in hamsters via pineal-independent processes [1].

SIBERIAN HAMSTERS

Siberian or Djungarian hamsters *(Phodopus sungorus sungorus)* exhibit a seasonal body weight cycle that is opposite to that of Syrian hamsters even though both species share the characteristic of gonadal regression after short photoperiod exposure [62]. Thus, Siberian hamsters reduce their body mass in short photoperiods from their long day maximum of approximately 40 to 45 g to a short day minimum of 30 to 35 g [51, 59, 104, 123]. Daily afternoon subcutaneous injections of melatonin mimic the effects of short photoperiods on body weight loss and food intake (Fig. 7) [119]. Similar to Syrian hamsters, Siberian hamsters exhibit "spontaneous" recrudescence of the gonads following extended short photoperiod exposure and increase their body weight [123]. These changes in body weight are primarily reflected as changes in body fat [123]. Male meadow voles *(Microtus pennsylvanicus),* like Siberian hamsters, also show a short photoperiod-induced decrease in body weight, but achieve their reduced body mass by decreasing all carcass components (females primarily decrease carcass lipid [25]). This body weight response to short photoperiods in Siberian hamsters seems to be inappropriate. These animals reduce their carcass energy reserves at a time when ambient temperature and food supply would both be decreasing as the harsh Siberian winter arrives. In addition, this decrease in body mass would increase the surface area to volume ratio and increase heat loss [78]. However, a number of other factors must be considered. First, with a reduced metabolic mass, a decrease in energy intake might be required for maintenance of the animal and indeed, a 30% reduction in caloric intake is seen in short photoperiod-housed male and female Siberian hamsters [2,123]. Second, short but not long photoperiod-housed hamsters exhibit daily
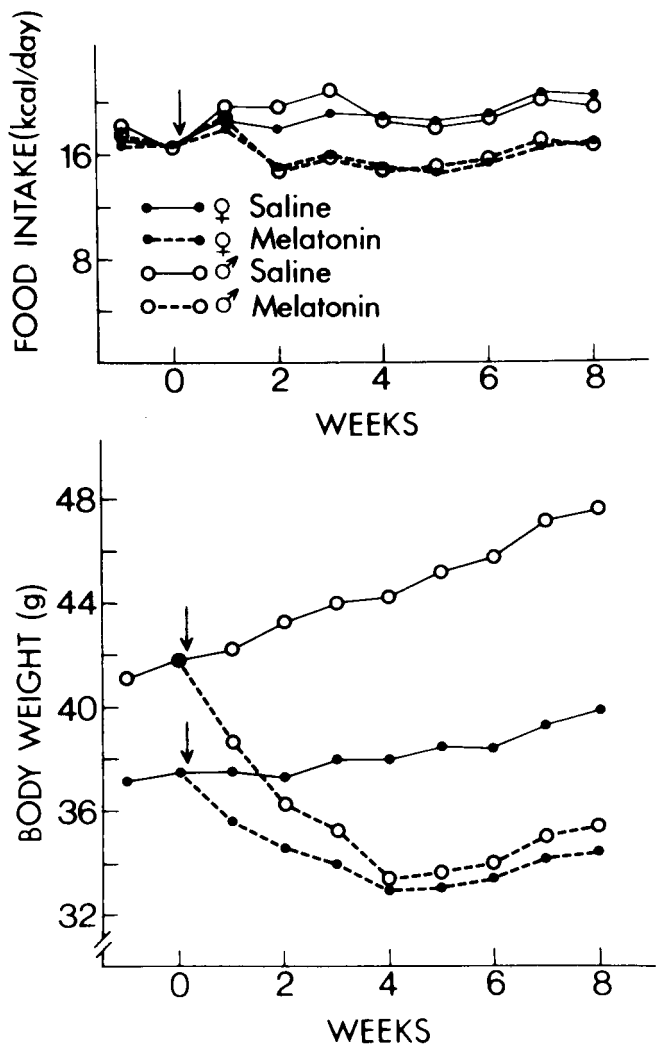

FIG. 7. Food intake and body weight of male and female Siberian hamsters given melatonin injections (12.5 μg/day SC, 3 hours before lights-out) or with the saline vehicle. All animals were housed in a LD 16:8 (long photoperiod). Arrow indicates the start of injections (Reprinted with permission from The American Physiological Society [123]).

torpor, where body temperature is reduced to approximately 17°C for up to eight hours resulting in a small, but reliable, energy savings [51]. Third, short photoperiod-housed hamsters have increased cold tolerance relative to their long photoperiod-housed counterparts, due in part to changes in pelage [51] and to increases in the thermogenic capacity of brown adipose tissue [49–53, 77, 103]. It is also possible that the insulative property of subcutaneous white adipose tissue is maintained or perhaps even increased in these animals based on our incidental observation of no observable abdominal fat, a clearly reduced carcass lipid content, but a remaining high carcass lipid content (~25%) relative to meadow voles [25] or Syrian hamsters [1,122] at their body weight nadirs. Finally, field studies in Siberia indicate that these hamsters are avid hoarders of seeds, perhaps countering the depletion of body energy stores by their stores of food in their burrows (Katherine Wynne-Edwards, personal communication).

FIG. 8. Carcass composition of male and female Siberian hamsters given melatonin injections (12.5 μg/day, SC, 3 hours before lights-out) or the saline vehicle for 8 weeks (Reprinted with permission from The American Physiological Society [123]).

Siberian hamsters do not fatten when fed the vegetable shortening-based high fat diet [121]. However, after long-term maintenance on a sunflower seed diet a slight obesity has been observed (Gehard Heldmaier, personal communication). This relative resistance to obesity may be adaptive if these animals are naturally seed eaters, particularly in the late summer and autumn. If it is important for Siberian hamsters to lose weight in the autumn, then high-fat diet-induced weight gains would be counterproductive. Meadow voles, another species which loses weight in the autumn, do not gain weight on a high-fat diet (John Dark and Irving Zucker, personal communication). Perhaps autumn-fattening species (e.g., Syrian hamsters) are particularly prone to dietary obesity, whereas species which lose weight in the autumn (e.g., Siberian hamsters and meadow voles) are not. However, Siberian hamsters are not totally unresponsive to the vegetable shortening-based high-fat diet. When exposed to short photoperiods, fat-fed female Siberian hamsters lost more weight than chow fed control animals [77]. This diet did not affect body weights of hamsters kept in long photoperiods. Thus, it is possible that body weight responses to photoperiod are exaggerated in both Syrian and Siberian hamsters when they are fed lipid-rich diets, even though one species gains and the other loses weight. If these animals are mainly seed eaters, then their natural diet undoubtedly contains more lipid than most carbohydrate-rich commercial rodent chows (typically only 4–6% lipid).

The decrease in body weight in short photoperiod-housed Siberian hamsters precedes the decrease in food intake by two to three weeks [23] suggesting a metabolic basis for the weight loss, perhaps via the increased metabolic activity of brown adipose tissue known to develop after short day exposure [77]. It is unlikely that the decrease in body weight is due to increased locomotor activity, because simulation of short photoperiods by afternoon melatonin injections decreased body weight and carcass lipid but did not change voluntary wheel-running [2], although the caveat of comparing home cage activity to running-wheel activity applies here as well.

Unlike the situation in Syrian hamsters it is clear that the pineal gland and, more specifically melatonin, is responsible for the changes in body weight in this species. Thus,

pinealectomy blocks the short photoperiod-induced decrease in body weight [115], gonadal regression [59, 60, 64], pelage color change [61] and daily torpor [115]. Conversely, appropriately timed afternoon systemic injections of melatonin in long photoperiod-housed hamsters mimic the naturally-occurring, short photoperiod-induced decrease in body weight (Fig. 7), carcass lipid (Fig. 8), food intake [2,123], and induce gonadal regression [2, 123, 130] and pelage color change [31].

These weight-regulatory mechanisms appear to respond to photoperiod even when energy balance is artificially disturbed. Steinlechner et al. [104] housed Siberian hamsters under natural photoperiod illumination and fed them ad lib or gave them a restricted food ration to produce a decrease in body weight. The restricted feeding was done at two times of the year, during summer when body weight is elevated, and during winter when it is depressed. In both cases restricted feeding decreased body weight. Upon refeeding, both groups of animals not only rapidly gained weight but returned to the body weight level appropriate for the current time of year, as exhibited by their ad lib-fed counterparts. Thus, the mechanism that naturally controls body weight gain or loss continued to monitor the progression of the photoperiod during the inhibition of the photosensitive body weight response and, upon disinhibition, rapidly returned body weight to the appropriate level for that time of year [104]. Since it is the photoperiodic control of the nocturnal duration of melatonin secretion that is responsible for body weight change in this species (see above), then it would seem reasonable to speculate that the mechanism governing seasonal change in melatonin secretion was still operating during the food restriction period, and that upon refeeding, the full expression of the melatonin-mediated control of body weight was manifested. Thus, Siberian hamsters have an ongoing monitoring of the change in photoperiod, perhaps by utilizing the change in the duration of melatonin secretion as a signal for their timekeeping mechanism. If the direction of the change is of prime importance, then within some limits, it might be predicted that the so called "critical" daylengths for photoperiod interpretation might be labile, reflecting the recent photoperiodic history of the animal. Indeed, Hoffmann [66] recently demonstrated the responses of the reproductive sys-

tem, body weight and pelage to a photoperiod of 14 hours light and 10 hours dark (LD 14:10), a daylength that would occur naturally in both the spring and fall, is dependent upon the previous photoperiod history of the animals. Following a long photoperiod, the LD 14:10 photoperiod was interpreted by Siberian hamsters as a short day (a progression from "summer to fall"), and following a short photoperiod it was interpreted as a long day (a progression from "spring to summer").

Gonadectomy, like short photoperiods, decreases body weight in male and female Siberian hamsters [123]. Furthermore, castrated male hamsters, like their intact controls, decrease their body weight following short photoperiod exposure. However, in ovariectomized hamsters, body weight is not further reduced by short photoperiods, although their intact counterparts exhibit the expected decrease in body weight, again, as reflected by a decrease in body fat [123]. This failure of ovariectomized hamsters to further decrease body weight following short photoperiod exposure suggests that when carcass lipid is reduced to some critical level it is, in some sense, defended. This defense might have adaptive value in not allowing energy stores to become severely depleted such that the added energetic demands of overwintering would jeopardize the animals' chances of survival.

The testes, and presumably testosterone, have a role in the increase in body weight seen in male Siberian hamsters transferred from short to long days, a time when melatonin causes increases in testis weight in this species [63]. Intact, castrated and sham-operated Siberian hamsters exposed to natural short photoperiods and then transferred to long days all increase their body weight. However, the castrated animals gained only one-half of the weight of intact or sham-castrated animals, and this smaller weight increase occurred at a slower rate [62]. This suggests that testosterone is necessary for the complete restoration of body weight in long photoperiods following short photoperiod exposure. In preliminary experiments, we examined the effects of afternoon melatonin injections on body weight change in photoregressed or castrated male Siberian hamsters that were pinealectomized (Bartness and Goldman, unpublished observations). Pinealectomy under these conditions prevents the acceleration of testicular recrudescence induced by subsequent long photoperiod exposure [63]. After five weeks of daily injections, body weight and epididymal fat pad weights were significantly increased in melatonin-injected hamsters relative to their saline-injected controls regardless of whether they were gonadally intact or castrated. In intact animals, melatonin injections more than doubled paired-testis weights compared to the saline-injected controls. Thus, in this paradigm, gonadal status did not affect the long day-induced increases in body weight or adiposity. Therefore, the contribution of the gonads, in particular, testosterone, to body weight increases is variable and depends on the conditions under which it is studied. For example, in a test of the role of testosterone in short photoperiod-induced daily torpor, subcutaneous constant release testosterone implants (which produced long day levels of this hormone in short day-housed, castrated males) not only blocked daily torpor but increased body weight. Both of these responses reverted to their short photoperiod values after removal of the implant [115].

OTHER HAMSTER SPECIES

European hamsters *(Cricetus cricetus)* are photoperiodic (Irving Zucker, personal communication) and have a body weight cycle with a duration of about one year [15, 80, 81]. Limited information is available for Turkish *(Mesocricetus brandti)* and to an even lesser extent Chinese hamsters *(Cricetulus griseus)*. Turkish hamsters show very small changes in body weight even though they are morphologically very similar to Syrian hamsters. For example, long photoperiod-housed female Turkish hamsters exhibit modest high-fat diet-induced weight gains (4.75 g/week versus 6.25 g/week for fat-fed, female Syrian hamsters [1, 102, 122]). They also exhibit a concurrent hyperphagia (nearly 35% greater than chow-fed controls) seldom seen in fat-fed Syrian hamsters. In addition, opposite to Syrian hamsters, these fat-fed Turkish hamsters show increased resting oxygen consumption, a factor that might contribute to their resistance to high fat diet-induced obesity (Hamilton and Wade, unpublished observations). There are no published reports on the effects of photoperiod or melatonin injections on body weight and related measures in Turkish hamsters. In preliminary experiments, body weight remains relatively constant in these animals, regardless of the photoperiod (Bruce Goldman, personal communication) or following treatment with melatonin (Joan Hamilton, personal communication).

Chinese hamsters resemble Siberian hamsters in their body size. Certain inbred sublines of Chinese hamsters develop spontaneous diabetes mellitus (for review see [46]), the manifestation of which is accelerated and exaggerated by feeding a high fat diet [47]. This is an insulin-independent diabetes; therefore the majority of the animals survive for a sufficient time to allow examination of their response to photoperiod. These animals are interesting beyond the comparative study of seasonal body weight change in that it has recently been suggested that insulin plays a permissive role in the nocturnal rise in pineal melatonin content based on findings in streptozotocin-induced diabetic Syrian hamsters [19]. In a preliminary study, we fed Chinese hamsters a commercial diet high in fat content (11% by weight) and divided them into diabetic or normal groups based on urinary glucose and ketone body measurements. Hamsters from each group were housed in a long (LD 14:10) or short (LD 8:16) photoperiod. Both diabetic and nondiabetic animals decreased their body weight to the same extent in short photoperiods and did so at a rate and to a level similar to that of Siberian hamsters. In addition, both short photoperiod-housed diabetic and non-diabetic hamsters had significantly reduced paired testis weights (Billington, Bartness, Morley, Levine and Gerritson, unpublished observations). Thus, if pineal melatonin is responsible for the short photoperiod responses of Chinese hamsters, then insulin appears relatively unimportant in mediating melatonin secretion in this species, and these data appear to conflict with those from experimentally-induced diabetes in Syrian hamsters [19].

TARGET SITES AND MECHANISMS OF ACTION FOR MELATONIN

The target sites and mechanisms of action of melatonin in the mediation of reproductive status and body weight are unknown. Working under the assumption that a likely candidate for a target site of melatonin is the brain, more specifically the hypothalamus, it was shown that lesions of the SCN block short photoperiod-induced testicular regression in Syrian hamsters [97,105]. In addition, SCN lesions in Syrian hamsters with photoregressed testes causes testicular recrudescence [97]. Therefore, the SCN is a possible site of action for the effect of melatonin on the reproductive system. However, thrice daily melatonin injections given to Sy-

rian hamsters with SCN lesions produced gonadal regression [6] similar to that seen in pinealectomized hamsters treated with the same melatonin injection regime. The most parsimonious explanation for the effects of SCN lesions on short photoperiod-induced gonadal regression is a disruption of photic information essential for appropriate pineal function. However, support for the SCN as more than just an intermediate in the neurological link between the retina and the pineal comes from direct application of melatonin to the SCN in the photoperiodic white-footed mouse *(Peromyscus leucopus)*. The findings that melatonin specifically binds to rat hypothalamus [86] and that melatonin has been localized in the SCN using immunohistochemical techniques [12] prompted Glass and Lynch [41] to directly apply melatonin to the SCN using constant release implants. Implants in or near the SCN were able to induce gonadal regression, while implants in other brain regions (e.g., preoptic area, posterior hypothalamus, basal forebrain, cerebral cortex, midbrain, striatum) were largely ineffective. In addition Glass and Lynch [41] found that daily afternoon, but not morning, injections of melatonin into the SCN area in female white-footed mice caused a collapse of the reproductive tract. Unfortunately, body weight changes were not reported for any of these SCN studies, so the relevance of this structure for the photoperiodic control of body weight remains to be determined. However, *P. leucopus* might not be appropriate for examining the neural mechanisms involved in the photoperiodic control of body weight because body weight is relatively unaltered by changes in daylength in this species [68, 69, 76].

The PVN of the hypothalamus seems to be implicated in the transduction of the photoperiodic signal. This structure is part of the proposed complex neural connection between the retina and the pineal gland (see above). Lesions of the PVN in rats block the nocturnal rise in pineal melatonin content [71]. It was nearly simultaneously reported from three laboratories that lesions of the PVN or periventricular area in male Syrian hamsters blocked short photoperiod-induced gonadal regression and blinding-induced regression [37, 73, 89], but not the circadian rhythm of wheel-running [96]. It was also noted that body weight was increased in hamsters with PVN lesions [73]. We were interested in whether lesions of the PVN would also block the short photoperiod-induced increase in body weight in Syrian hamsters. Long photoperiod-housed, female Syrian hamsters with lesions of the PVN did not show any change in food intake or body weight for five weeks postlesion when fed a maintenance diet of commercial rodent chow. However, once fed a high fat diet, the hamsters with PVN lesions had an exaggerated increase in diet-induced obesity relative to their sham-lesioned controls. When half the animals were transferred to a short photoperiod, only hamsters with sham lesions of the PVN increased their body weight. In addition, the short photoperiod-induced disruption of estrous cyclicity [3] was seen in the control animals, but not the hamsters with PVN lesions. Therefore, the PVN appear to have roles in regulating body weight and reproductive status in both male and female Syrian hamsters [3, 73, 89].

Preliminary reports suggest that the role of the PVN is more than just a relay for photoperiodic information, and that the PVN may actually be a target site (Bartness and Wade, unpublished observations). Long photoperiod-housed, female Syrian hamsters had guide cannulas implanted above the PVN, ventromedial hypothalamic nuclei, or the lateral hypothalamus. Daily afternoon, pulsed melatonin infusions (400 ng) or the saline vehicle were given for six weeks. Although only a few animals were employed in each group, it was clear that only hamsters receiving melatonin infusions in the PVN exhibited short photoperiod-like increases in body weight. Estrous cyclicity, uterine weight and brown adipose tissue mass were not significantly affected by the melatonin infusions. Therefore, it is possible that the PVN is a target site for the action of melatonin on body weight, but it may affect the reproductive system as part of the transmission of photoperiod information to the pineal gland. Given the rapidly growing literature supporting a role of the PVN in rats as a site modulating food intake and body weight [74], it is tempting to suggest that this area may be performing a similar role in the context of a seasonal modulation of these responses in Syrian hamsters. The olfactory bulb has also been reported to be involved in short photoperiod-induced gonadal regression [90]. Olfactory bulbectomy blocked the short day-induced decrease in testes weight. However, this surgery elevates FSH secretion in both long and short photoperiods (Bruce Goldman, personal communication). Because elevations of this gonadotrophin are associated with testicular growth or maintenance, while decreases are associated with testicular regression (e.g., [18, 31, 109, 131]), the olfactory bulb may have an inhibitory role in FSH secretion and most likely is not a brain region directly involved with the photoperiodic control of reproductive status. The role of the olfactory bulb in the photoperiodic control of body weight has not been studied in Syrian or Siberian hamsters, but it has been reported that olfactory bulbectomy increases body weight in European hamsters regardless of the stage of the seasonal body weight cycle in which the surgery is performed [81].

To date, the study of target sites of action for melatonin using traditional receptor binding techniques has resulted in very limited success and perhaps even added confusion. For example, it is not clear whether the putative melatonin receptors that have been identified are found in the synaptosomal preparation of neural tissue [16] or in the cytoplasmic fraction [20]. In either case, the obstacle that appears to hamper any clear identification of the distribution of melatonin receptors has been the inability to obtain a high degree of specific binding (Eric Bittman, personal communication).

Finally, we have emphasized potential CNS sites of melatonin action. However, this does not preclude the possibility that melatonin might act directly upon other, nonneural, tissues, too. Radiolabeled melatonin is found in a wide variety of tissues following systemic administration [20]. Indeed, there is ample precedent among other hormones for concurrent action at multiple sites (both neural and nonneural) that may influence energy balance (e.g., estradiol and progesterone [45, 125, 126]).

SUMMARY AND CONCLUDING REMARKS

We have attempted to present what is currently known about the photoperiodic control of body weight, primarily with regard to Syrian and Siberian hamsters. The pineal gland and its hormone, melatonin, are clearly responsible for photoperiod-induced changes in body weight in Siberian hamsters and to some extent in Syrian hamsters. In Syrian hamsters, we have suggested that diet-, gonad-, thyroid-, and pineal/melatonin-dependent and -independent mechanisms may contribute to photoperiodic effects on body weight and related energy measures. In Siberian hamsters, we find no

pineal independent effects on these endpoints but modest gonad-independent and -dependent effects. For the pineal/melatonin-dependent effects in these two species, we find the same hormone (melatonin) producing opposite effects on body weight (increases in Syrian and decreases in Siberian hamsters), but doing so primarily by altering the same carcass component (lipid).

It is unclear why one species of hamster should possess pineal-independent mechanisms mediating seasonal weight changes when the other species does not. One might speculate that it has something to do with the fact that Syrian hamsters gain weight in short photoperiods. Perhaps a failure to gain weight in the autumn would be more life-threatening for a Syrian hamster than a failure to lose weight would be for a Siberian hamster. Thus, Syrian hamsters may have evoled multiple, independent mechanisms to assure appropriate adaptive changes in energy metabolism prior to the onset of winter. Note that other autumn-fattening species (e.g., ground squirrels, mink) exhibit seasonal fattening in the absence of a pineal gland ([133], Martinet, personal communication).

Comparative studies using several hamster species may help unravel the mystery surrounding the mechanism(s) by which melatonin or photoperiod can alter body weight and energy metabolism. The study of seasonal obesity may provide fundamental knowledge concerning the influence of environmental factors on obesity and also may provide information about the various strategies of energy metabolism in species with differing ecological niches.

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