MINIREVIEW

Seasonal Changes in Adiposity: the Roles of the Photoperiod, Melatonin and Other Hormones, and Sympathetic Nervous System

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It appears advantageous for many non-human animals to store energy body fat extensively and efficiently because their food supply is more labile and less abundant than in their human counterparts. The level of adiposity in many of these species often shows predictable increases and decreases with changes in the season. These cyclic changes in seasonal adiposity in some species are triggered by changes in the photoperiod that are faithfully transduced into a biochemical signal through the nightly secretion of melatonin (MEL) via the pineal gland. Here, we focus primarily on the findings from the most commonly studied species showing seasonal changes in adiposity—Siberian and Syrian hamsters. The data to date are not compelling for a direct effect of MEL on white adipose tissue (WAT) and brown adipose tissue (BAT) despite some recent data to the contrary. Thus far, none of the possible hormonal intermediaries for the effects of MEL on seasonal adiposity appear likely as a mechanism by which MEL affects the photoperiodic control of body fat levels indirectly. We also provide evidence pointing toward the sympathetic nervous system as a likely mediator of the effects of MEL on short day-induced body fat decreases in Siberian hamsters through increases in sympathetic drive on WAT and BAT. We speculate that decreases in the SNS drive to these tissues may underlie the photoperiod-induced seasonal increases in body fat of species such as Syrian hamsters. Clearly, we need to deepen our understanding of seasonal adiposity, although, to our knowledge, this is the only form of environmentally induced changes in body fat where the key elements of its external trigger have been identified and can be traced to and through their transduction into a physiological stimulus that ultimately affects identified responses of white adipocyte physiology and cellularity. Finally, the comparative physiological approach to the study of seasonal adiposity seems likely to continue to yield significant insights into the mechanisms underlying this phenomenon and for understanding obesity and its reversal in general.

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Obesity in humans is a disease of figuratively and literally enormous proportions. The secondary health consequences of obesity include cardiovascular disease, stroke, noninsulin-dependent diabetes mellitus, and carcinomas (reviewed in Ref. 1). Because of these secondary health consequences, there seems to be little survival advantage for humans to eat and store as much energy as possible in lipid reserves, especially when the food supply is relatively constant and plentiful as it is in most economically developed countries. It has been hypothesized that a contributing factor to the prevalence of obesity in contemporary society is the persistence of metabolically efficient systems for storage of energy as body fat (2). In contrast to humans, it appears advantageous for many nonhuman animals to store energy body fat extensively and efficiently because their food supply is more labile and less abundant than in their human counterparts. The level of adiposity in many of these species does not continuously increase across their life span, however; instead, body fat levels often shows predictable increases and decreases with changes in the season. Species exhibiting seasonal adiposity can be divided into two major categories. The first category includes species that respond to changes in the photoperiod (daylength; e.g., hamsters and voles), some of which will be

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the primary focus of this review, whereas the second category includes species that respond to the timing of an endogenous "clock" of unknown location (e.g., ground squirrels, wood chucks, and marmots), that will not be our focus (reviewed in Ref. 3). Species in both categories appear to shift from the obese to the lean state effortlessly, unlike humans. We will focus on the possible mechanisms underlying photoperiod-induced seasonal adiposity cycles.

Animals Display Seasonal Changes in Physiology and Behavior, Especially in Temperate Zones

Animals living in temperate zones frequently show seasonal changes in a host of physiological and behavioral responses. For example, the timing of reproduction is critical to many small rodent species living in temperate zones. Most of these species are reproductively quiescent in the late fall/winter, when ambient temperatures decline and food availability is typically low, and they resume reproductive activities in the early spring/summer when ambient temperature and the food supply are more favorable (reviewed in Ref. 4). Although photoperiod-induced changes in seasonal adiposity occur in a variety of mammalian species, they have been studied most extensively in Syrian (*Mesocricetus auratus*) and Siberian hamsters (*Phodopus sungorus*; reviewed in Refs. 5 and 6); therefore, these species will be highlighted throughout this review. The seasonally adaptive changes in lipid stored in white adipose tissue (WAT, the major energy storage depot for mammals; 7), and in thermogenesis by brown adipose tissue (BAT, an important site for heat generation in mammals; 8), often takes weeks or months to be manifested fully. Therefore, it appears that natural selection has favored animals that accurately begin the appropriate changes in these tissues, as well as those more directly associated with reproduction, in anticipation of the forthcoming season.

The photoperiod is the critical environmental cue that triggers many seasonal responses and it is transduced into a biochemical signal by the pineal gland. The change in the photoperiod (daylength) is the most noise-free signal in the environment indicating the forthcoming season (9). Therefore, by simply changing the photoperiod in the laboratory, the entire constellation of photoperiodic responses in nature can be conveniently mimicked and manipulated (4, 10). For example, hamster and vole species will show the full complement of short-day (SD) "winter-like" responses if the daylength is significantly shortened from a long-day (LD) "summer-like" photoperiod (11–15). Procedurally, this often is done by switching animals from a 16:8-hr or 14:10-hr light:dark cycle to an 8:16-hr or 10:14-hr light:dark cycle.

This photoperiod cue is received by the retinal ganglion cells and is transmitted through a multisynaptic pathway to the pineal gland (16). Interruption of this circuit at any point, including the eyes or the pineal, blocks the effects of SDs on the reproductive system (17) and most other seasonal responses, including the seasonal changes in adiposity (11, 18). For example, pinealectomy blocks the photoperiod-dependent changes in body and lipid mass in Syrian hamsters (11), although evidence for a photoperiod-induced, pineal-independent effect also has been reported (11, 19). Pinealectomy also blocks the seasonal changes in body and lipid mass of Siberian hamsters (18, 20, 21) and meadow voles (22, 23). Once the neurochemical interpretation of the photoperiod reaches the pinealocytes via its sympathetic nervous system (SNS) innervation, it is transduced into an endocrine signal in the form of the rhythmic secretion of the melatonin (MEL) into the blood. Pineal and plasma MEL concentrations are at their nadir during the light phase of the photocycle and at their peak during the dark phase (reviewed in Refs. 24 and 25). This pattern of MEL synthesis and secretion results from the regulation of the pineal gland by an endogenous circadian oscillator that is entrained to the light:dark cycle (26). Thus, the duration of the night is faithfully coded into the duration of MEL secretion and serves to trigger seasonal responses—long MEL secretion durations signal "fall/winter," whereas short MEL secretion durations signal "spring/summer" (reviewed in Ref. 25).

The peak duration of MEL secretion is its critical feature for triggering SD responses. This was initially shown by giving daily subcutaneous injections of MEL to LD-housed, pineal-intact Syrian or Siberian hamsters ~2 to 3 hr before lights out (i.e., the "timed afternoon injection paradigm"; 27). Hamsters treated in this manner exhibited SD-like seasonal changes in body and lipid mass (11, 28, 29) and in reproductive status (30–32). Why does this happen? One notion is that the exogenously administered MEL summates with the nocturnally secreted endogenous MEL to lengthen the peak duration of circulating MEL, thereby approximating those occurring naturally in SDs (reviewed in Ref. 25). This critical nature of the duration of MEL secretion for triggering photoperiod-induced changes in adiposity and reproductive status was later unequivocally shown by giving LD-housed, pinealectomized Siberian or Syrian hamsters, or sheep, precisely timed daily subcutaneous MEL infusions instead of bolus injections (i.e., termed the "timed infusion paradigm") so as to mimic the naturally occurring peak durations of circulating MEL in SDs (reviewed in Ref. 25). For example, long-duration MEL infusions triggered SD-like decreases in body mass and fat, and gonadal regression in adult male Siberian hamsters (21, 33, 34).

MEL Receptors Occur in the Brain and Periphery, but Stimulation of Specific Central Sites Appears Necessary for Seasonal Changes in Adiposity and Reproductive Status

MEL brain receptors were first suggested by the binding of a radioactive MEL analogue (2-[^{125}I]iodomelatonin; IMEL) to neural tissue (reviewed in Refs. 35–37). Only a relatively few brain MEL binding sites exist (38, 39), although MEL binds extensively to many peripheral tissues

(e.g., 40–44). IMEL binds in the brains of a wide range of mammals (e.g., sheep, deer, goats, rabbits, laboratory rats, Syrian, Siberian, and European hamsters, white-footed mice, golden-mantled ground squirrels, Guinea pigs, nine-banded armadillos, and humans), as well as non-mammals (Atlantic hagfish, lamprey, hedgehog skates, rainbow trout, clawed toads; reviewed in Ref. 35). Across many mammalian species, one brain and one peripheral site consistently show IMEL binding—the suprachiasmatic nucleus of the hypothalamus (SCN) and the pars tuberalis (PT) of the pituitary gland (45–48), respectively. Many of these species show binding in both the SCN and the PT, although there are a few seasonally breeding species where IMEL binding only is found in the PT (49, 50). Gene expression for one of the MEL receptor subtypes, the MEL 1_a receptor (also known as the mt_1 receptor) is present in the SCN and PT of Siberian hamsters and laboratory rats (51). The MEL 1_a receptors of the SCN are important for the seasonal changes in reproductive status and adiposity in at least Siberian hamsters. Thus, daily SD-like MEL signals given via the timed-infusion paradigm to pinealectomized Siberian hamsters bearing SCN lesions (33, 34, 52), do not trigger SD-like decreases in body and WAT pad masses, as well as gonadal regression. In Syrian hamsters, however, SCN lesions do not block SD-like MEL-induced gonadal regression (53). In addition, infusions of MEL directly into the SCN of juvenile Siberian hamsters inhibit maturation of the reproductive system, mimicking the effects of SD exposure in these animals (54).

The SCN output pathways (efferents) important for relaying the photoperiod-encoded MEL signals to other brain/peripheral targets involved in seasonal responses are unclear at present (reviewed in Ref. 55). It appears MEL works via an intermediary, at least for the seasonal changes in adiposity, because WAT lipolysis (fat mobilization) and lipogenesis (fat synthesis) are not triggered in isolated adipocytes using physiological doses of MEL in Syrian hamsters, laboratory rats, and rabbits (56). According to a recent report, however, lipolysis is inhibited by MEL *in vitro* in laboratory rat inguinal, but not epididymal WAT (57). Furthermore, MEL can act directly on Siberian hamster BAT cells through a MEL-specific binding site (but not the MEL_{1a} receptor isoform; 44), as well as modulating BAT mitochondrial cytochrome b gene expression directly (58). Thus, although there are some direct effects of MEL on its peripheral target adipose tissues via its receptors, the preponderance of evidence suggests that the MEL signal is received by brain MEL receptors.

The means by which the season-encoded MEL signal reaches peripheral tissues after stimulating central MEL receptors is not well understood. How stimulation of these receptors ultimately affects peripheral tissues is not certain at this time. One possible means by which MEL ultimately affects adipose tissues, gonads, hair follicles, and other peripheral endpoints that change seasonally involves projections from neurons within the SCN and/or other brain sites that possess MEL_{1a} receptors to these target tissues via a humeral intermediary. Alternatively, stimulation of the brain MEL receptors may trigger the seasonal changes in these tissues strictly through neural communication of the photoperiod-encoded MEL signals.

Do the Hormones that Fluctuate Seasonally Mediate Photoperiod-Induced Changes in Adiposity?

Although there are many candidates for the hormonal intermediary controlling the photoperiod (MEL) effects on seasonal adiposity (for a more complete review, see Ref. 6), the supporting data for such a humoral intermediary are few. Here we discuss possible roles of gonadal steroids, prolactin, thyroid hormones, glucocorticoids, insulin, glucagon, and leptin in mediating seasonal adiposity in Siberian and Syrian hamsters.

Gonadal Steroids. Hamsters (12, 59–61), voles (15, 62), collared lemmings (63), and deer mice (64, 65) all regress their gonads in response to SD exposure; however, their body and lipid mass responses differ (see below). That is, SD-exposed collared lemmings (66), prairie voles (14), and Syrian hamsters (11, 67, 68), increase, whereas SD-exposed Siberian (12, 13, 61, 69, 70) and European hamsters (60), meadow voles (15, 71), and deer mice (72, 73) decrease their body and lipid mass. Across these and many other rodent species, the direction of the SD-induced change in adiposity can be predicted by the effects of gonadectomy on the body fat levels of LD-housed individuals of these species. This lead to the speculation that the effects of gonadectomy and the SD-induced "functional gonadectomy" on body fat are both primarily due to the decreases in testosterone and estrogen. For example, LD-housed female Syrian hamsters (74, 75), female collared lemmings (66), and male prairie voles (14) increase their body and lipid masses when they are gonadectomized as well as when they are "photoperiodically gonadectomized" by SDs (11, 14, 66). In contrast, Siberian hamsters (13, 76), male deer mice (77), meadow voles (71, 78), and European hamsters (60, 79) decrease their body and lipid masses when gonadectomized and also decrease body and lipid masses when exposed to SDs (60, 69, 79).

Because gonadectomized animals exposed to SDs have body fat increases or decreases that are similar to their SD-exposed gonad-intact counterparts, this obvious explanation for the effects of SD exposure on seasonal adiposity is not satisfactory. That is, the gonadectomy-induced decrease in body fat of LD-housed Siberian hamsters is decreased further when they are subsequently exposed to SDs (13), and the gonadectomy-induced increase in body fat of LD-housed Syrian hamsters is increased further when they are subsequently exposed to SDs (11). In addition, body and lipid mass (along with all other photoperiodic responses) revert to their characteristic LD values after transfer from SDs to LDs or after extended exposure to SDs (i.e., "spontaneous recrudescence"), and these changes in body and

lipid mass also are partly independent of the gonadal responses. Thus, when ovariectomized Syrian hamsters (28), castrated male European hamsters (60), castrated male meadow voles (71), and cold-exposed castrated male Siberian hamsters (81) are exposed to persisting SD exposure, their species-specific SD-induced increases or decreases in body and lipid mass are reversed despite being gonadectomized. In addition, if SD-housed castrated male Siberian hamsters at their body mass nadir are abruptly shifted to LDs, they show a nearly identical increase in body mass compared with SD-housed testes-intact hamsters experiencing identical changes in the photoperiod (82). Therefore, the effects of the photoperiod on gonadal steroid secretion and action are not primarily responsible for seasonal changes in body mass and fat in these animals.

Prolactin. All species that show photoperiod control of reproductive cycles, regardless of whether they are LD or SD breeders (83), show SD-induced decreased prolactin (PRL) serum concentrations (84). An important role for PRL in the photoperiodic regulation of lipid deposition or mobilization has not been clearly demonstrated, but PRL is capable of altering WAT lipid metabolism both *in vivo* and *in vitro* in laboratory rats (85, 86). Syrian and Siberian hamsters show the typical SD-induced decreases in serum PRL concentrations (87). Tests of the role of PRL in seasonal obesity have largely been negative. For example, injections of the dopamine receptor agonist bromocryptine (CB-154), an inhibitor of PRL secretion (88), designed to produce SD PRL levels in LD-housed Syrian or Siberian hamsters does trigger their species-specific SD increases or decreases in changes in lipid mass or WAT metabolism, respectively but not to the same degree as SDs (89). Conversely, LD pituitary explants or infusions of ovine PRL designed to produce LD serum concentrations of PRL in SD-housed Syrian and Siberian hamsters, respectively, do not revert them to their species-specific LD levels of body fat (89, 90). Therefore, at least in Syrian and Siberian hamsters, it does not appear that PRL per se is a significant mediator of photoperiod-induced changes in body and lipid mass. It should be noted, however, that a critical role for PRL in the development of photoperiod-induced seasonal changes in body fat (91–95) has been reported by one laboratory, although it is not supported by others (89, 96).

Thyroid Hormones. The pineal gland and MEL modulate the neuroendocrine-thyroid gland axis in several species and consequently, the secretion of thyroxine (T_4) and triiodothyronine (T_3) (reviewed in Ref. 97). SD exposure significantly decreases serum concentrations of T_4 and T_3 in Syrian hamsters (98, 99) and collared lemmings (100, 101) and more modestly in Siberian hamsters (102–104). These SD-induced reductions in thyroid hormones are somewhat surprising because "winter-like" SDs would typically be associated with decreases in ambient temperature in the wild, and most rodent species increase their secretion of thyroid hormones in response to cold exposure (105, 106). It may be that the neuroendocrine-thyroid axis is only stimulated when animals actually experience the cold, but not in preparation for cold exposure. Indeed, SD exposure alone only produces a transient increase in T_3 in Syrian hamsters with no enduring effects (107). The photoperiod via MEL does seem important in BAT thermogenesis, however, in that MEL treatment stimulates type-II thyroxine 5′-deiodinase in BAT, the enzyme responsible for local tissue conversion of T_4 to T_3 (105). Moreover, increases in deiodination of T_4 facilitate BAT UCP-1 gene expression in the cold (106). Thus, thyroid hormones may be important for the SD increase in BAT thermogenesis, but seem to require the addition of cold to be maximally effective. The role of thyroid hormones in mediating the photoperiod-induced changes in adiposity, however, is less clear. For example, SD-housed male Siberian hamsters given daily T_4 injections have LD-like, high serum T_4 and T_3 concentrations, yet show decreases in body, fat pad, and paired testes masses that are similar to those of SD-housed vehicle- and noninjected hamsters (104). Therefore, photoperiod/MEL-induced changes in thyroid hormones do not to seem have a major role in the seasonal control of body and lipid mass, at least in these hamster species.

Glucocorticoids. The role of the glucocorticoids in the photoperiod/MEL-controlled alterations in energy balance has not been thoroughly investigated; however, the role of glucocorticoids in all aspects of energy balance, including food intake, lipid mobilization and storage, and thermogenesis is well established in several categories of rodent obesity (dietary, genetic, endocrine, and hypothalamic; 108). A relation between glucocorticoid secretion and the photoperiod has been shown for some of the species discussed above. For example, Syrian (99, 109) and Siberian hamsters (110), prairie voles (111), and collared lemmings (101) show seasonal changes in serum cortisol and/or corticosterone concentrations or changes in both (note that unlike laboratory rats [112, 113] or humans [114], hamsters have significant serum concentrations of both cortisol and corticosterone concentrations [99, 109, 110, 115]). The effects of adrenal glucocorticoids on WAT mass and function may be mediated by the Type II glucocorticoid receptor found in the cytosol of WAT adipocytes (116). Decreases in glucocorticoid secretion and/or decreases in activation of Type II glucocorticoid receptors via adrenalectomy is not feasible in Siberian hamsters because the additional loss of mineralicorticoids by this surgery does not trigger increases in salt appetite as it does in laboratory rats and mice, thereby leading to their death (T. Bartness and B. Goldman, unpublished data). Therefore, to study the possible role of glucocorticoids in hamsters a different tact is needed.

First, although glucocorticoids promote adiposity in the typically studied rodent obesity models, it seemed possible that they might produce an opposite effect in Siberian hamsters, given the obesity promoting effects of estrogen and testosterone in this hamster species (76, 117). Therefore, Type II glucocorticoid receptor blockade by RU-486 (RU-

486 is not an progestin receptor antagonist in hamsters; 118) was used to produce a SD-like inhibition of glucocorticoid function in LD-housed hamsters. LD-housed Siberian hamsters treated chronically with RU-486 for several weeks did not decrease body and lipid mass as occurs when they are transferred from LDs to SDs (110). Thus, unlike the inhibition of obesity by Type II glucocorticoid receptor blockade using RU-486 in genetic- and diet-induced obese laboratory rats (119, 120), these receptors, and perhaps glucocorticoids in general, do not seem to be a primary factor in the photoperiodic control of seasonal body and lipid mass cycles in this species and perhaps in other photoperiodic species.

Insulin and Glucagon. Of the species showing photoperiod-induced change in adiposity, seasonal fluctuations of serum insulin concentrations only have been measured in Syrian and Siberian hamsters to our knowledge. Specifically, SD exposure decreases serum insulin concentrations in Siberian hamsters (115), but increases serum insulin concentrations in Syrian hamsters (92–94, 121). In Siberian hamsters, serum insulin concentrations decrease by 4-fold in SDs compared with LDs (115), consistent with the positive correlation between circulating insulin concentrations and level of adiposity in most mammals (reviewed in Ref. 122). Despite this relation, normal SD-induced decreases in body and lipid mass, food intake, and gonadal regression are seen in Siberian hamsters treated with streptozotocin to induce diabetes mellitus and then one of several levels of insulin replacement to produce a wide range of serum insulin concentrations (123). These data suggest that insulin status does not play a major role in the photoperiodic control of seasonal adiposity, at least for this species.

Insulin also has been manipulated experimentally in Syrian hamsters, but indirectly, to test for its role in SD-induced body fat increases (121). That is, the neural control of insulin secretion by the parasympathetic nervous system was eliminated by total subdiaphragmatic vagotomy. This treatment blockaded the SD-induced increases in body and lipid mass characteristic of this species, but did not block gonadal regression (121). Interpretation of these data is difficult, however, because total subdiaphragmatic vagotomy causes a multitude of effects (124) in addition to the blockade of neurally released insulin. Therefore, the inability of vagotomized Syrian hamsters to increase body mass when exposed to SDs does not necessarily lend support for a role of insulin in the SD-induced obesity of this species.

Although the pancreatic and intestinal hormone glucagon is well known for its stimulation of WAT lipolysis and of BAT thermogenesis, to our knowledge, serum concentrations of glucagon have not been measured in any of the rodent species showing photoperiod-mediated changes in seasonal adiposity. It seems quite likely, however, that glucagon may play a significant role in the photoperiodic control of energy balance because it stimulates BAT thermogenesis (125), is an important hormone in the thermogenic response to the cold (126), and has receptors on WAT adipocytes (127). Thus, in species showing SD-induced decreases in adiposity, such as Siberian hamsters, SD increases in glucagon secretion, which show a reciprocal relation with insulin (128), could increase lipid mobilization from WAT and also could increase the thermogenic capacity of BAT, whereas in species showing SD-induced increases in adiposity, such as Syrian hamsters, the opposite might occur. This intriguing notion remains to be tested.

Leptin. In virtually all mammalian species undergoing seasonal fluctuations in body fat, there are concomitant fluctuations in circulating leptin, a peptide hormone produced primarily, but not exclusively, by WAT (reviewed in Refs. 129 and 130). Because both leptin and its receptors are integral components of a hypothesized feedback system that regulates body fat levels (reviewed in Ref. 131), leptin also may be involved in seasonal control of body fat. According to the commonly accepted, leptin feedback system hypothesis, as an animal gets fatter, more leptin is secreted from the growing adipose depots. The resulting increases in concentrations of circulating leptin stimulate brain (and other) leptin receptors informing the brain of overall adiposity levels. In turn, the brain triggers compensatory changes to counter the increases in body fat, such as decreased energy intake and/or increased energy expenditure. Of course, if this hypothesized system functioned in this simplistic way, then no animals would become obese unless there are defects in the system. Indeed, defects do exist, as is most markedly seen in *ob/ob* and *db/db* mice that either do not synthesize leptin or do not have the long isoform leptin receptor, respectively (reviewed in Refs. 130–133). Regarding seasonal adiposity and Siberian hamsters, this hypothesized leptin feedback system, as typically conceived, is at odds with physiological reality. That is, although SD-exposed Siberian hamsters have decreased body fat and accordingly decreased WAT leptin mRNA (135–137) as well as circulating leptin concentrations (135, 138, 139), they have a concomitant decrease in food intake (13, 140, 141) rather than the predicted increase in food intake that would be expected from this leptin feedback model. Finally, the long isoform of the WAT leptin receptor gene expression also is reduced in the arcuate nucleus, a key integrative hypothalamic area for energy balance, in SDs compared with LDs (136), despite a predicted upregulation of the receptor according to many current notions regarding leptin and food intake.

The effects of exogenous leptin on body and lipid mass and food intake have also been examined in Siberian hamsters. Specifically, chronic leptin administration reverses the SD-induced decrease in food intake of Siberian hamsters to levels comparable with LD-housed controls not injected with leptin, but do not affect the food intake of their fatter LD-housed counterparts (142). This contrasts to the inhibition of food intake by leptin administration to genetically obese mice (*ob/ob* that are leptin-deficient; 143–146), but is consistent with decreased sensitivity to the suppression of

food intake by leptin of diet-induced obese AKR/J (147). In contrast to the above results in Siberian hamsters given leptin, another study report that leptin reduces body and lipid mass to a greater extent in SDs compared with LDs, but reduces food intake similarly in both photoperiods (135). The likely differences between these studies and those mentioned earlier may be due to differences in leptin administration that is critical for its effects on food intake and body fat (143, 148), as well as other methodological considerations (discussed in Ref. 142). Nevertheless, it appears that the effects of leptin on energy balance may be contingent upon the current photoperiod exposure. Therefore, seasonal changes in circulating leptin concentrations, coupled with changes in leptin sensitivity, may serve as part of an adaptive mechanism for increasing the odds of winter survival when food availability is decreased and adipose tissue stores are at their nadir.

Summary of Possible Humeral Factors Mediating Levels of Seasonal Adiposity. Finally, in terms of hormonal mediators of photoperiod/MEL-induced changes in obesity, it is possible that changes in several hormones working in combination are necessary to produce seasonal adiposity changes mediated by the photoperiod/MEL, and this may explain the difficulty in ascribing the SD-induced changes in adiposity to a single hormone. The ability to mimic accurately the natural secretion profiles for multiples of these hormones is difficult or impossible. Alternatively, it may be that MEL signals affect WAT and BAT via its innervation through the sympathetic nervous system (SNS) outflow from brain to fat and thereby modulate seasonal adiposity via this mechanism.

The SNS May Modulate Seasonal Adiposity

WAT and BAT are both innervated by the SNS; (reviewed in Refs. 149–152). Whereas the innervation of BAT by the SNS has been undisputed and known for over 30 years (153), the innervation of WAT by the SNS has been more controversial and, to date, no convincing evidence exists for parasympathetic innervation of WAT (reviewed in Ref. 152). Although the neuroanatomical evidence for the SNS innervation of WAT was suggested over 100 years ago (154), and functional evidence for this innervation has been accumulating for nearly 90 years (155), some controversy about this innervation has continued until recently. The postganglionic sympathetic innervation of WAT was shown directly using retrograde and anterograde tract-tracing methods recently (156). Briefly, relatively separate populations of postganglionic neurons within the sympathetic chain corresponding to the thoracic and lumbar sections of the spinal cord was revealed for the inguinal WAT (IWAT) and epididymal WAT (EWAT) pads of Siberian hamsters (156). This study was prompted by an earlier finding showing that lipid was mobilized non-uniformly from WAT pads of SD-exposed Siberian hamsters (157). Specifically, the more internally located pads (i.e., EWAT and retroperitoneal WAT [RWAT]) show the greatest lipid mobilization after SD exposure, as reflected by their decreased mass, whereas the more externally located pads (i.e., IWAT) show the least lipid mobilization after SD exposure (76, 117, 157). The identification of relatively separate neuroanatomical pools of postganglionic SNS neurons innervating these pads supports a likely anatomical basis for this differential lipid depletion, perhaps due to differences in sympathetic drives. Indeed, norepinephrine turnover, an indicator of SNS drive (158), was greater in EWAT than in IWAT corresponding to the greater decrease in EWAT mass than IWAT mass after SD exposure in Siberian hamsters (156).

Although partially satisfying as a mechanism underlying SD-induced increases in lipid mobilization from WAT as well as the fat pad-specific differences in the degree of lipid mobilization by Siberian hamsters, the CNS origins of the SNS outflow from brain to WAT were unknown until recently. Fortunately, the ability to use viral tract tracers to define complete neural circuits within the same animal, developed through the pioneering studies of Card (159) and Loewy (160), made this possible. This was accomplished using an attenuated strain of the pseudorabies virus (PRV; Bartha's K strain) as a retrograde transneuronal viral tract tracer and applied by us to define the SNS outflow from brain to WAT and BAT in Siberian hamsters and laboratory rats (159–164). Briefly, the use of this virus as a transsynaptic retrograde tract tracer is possible because the virus is taken up into neurons following binding to viral attachment protein molecules found on the surface of neuronal membranes at the site of initial injection, in this case, WAT and BAT. These protein surface molecules act as "viral receptors." Neurons synapsing on the infected cells become exposed to relatively high concentrations of the virus particles that have been exocytosed. The virus particles are then taken up by synaptic contact. This process continues, causing an infection along a hierarchical chain of functionally connected neurons from the adipose tissues, in this case, to the farthest reaches of the forebrain (165, 166). The virus is visualized using standard immunocytochemical methods or more recently using viruses engineered to make green fluorescent protein (167–169).

Application of this viral technology to the study of the innervation of WAT and BAT has revealed more similarities than differences in the CNS origins of the SNS outflow from brain to these two adipose tissue types (161, 162). Specifically, infected cells occur at all levels of the neuroaxis for both adipose tissue types and include the sympathetic chain, the spinal cord (intermediolateral cell column and central autonomic nucleus), the brainstem (the classically defined sympathetic sites such as the lateral and gigantocellular reticular nuclei, caudal raphe area, C1 adrenaline and A5 noradrenaline cell regions, and nucleus of the solitary tract), the midbrain (central gray), and the forebrain (paraventricular nucleus [PVN], SCN, lateral and dorsomedial hypothalamic nuclei, medial preoptic area, arcuate

nucleus, bed nucleus of the stria terminalis, and lateral septum); for details of all involved structures and differences between WAT and BAT, see References 161 and 162. The lack of infections in the ventromedial hypothalamus (VMH) after PRV injections to either WAT or BAT is notable because of the dozens of physiological studies indirectly suggesting VMH-SNS-WAT and VMH-SNS-BAT circuits (reviewed in ref. 150). The PRV technique has also failed to provide neuroanatomical support for the notion of circuits involving the VMH in the SNS innervation of a host of tissues including the pancreas (170) and adrenal medulla (160, 171). Most likely, the reason for the discrepancy between the results of the non-neuroanatomical studies and those of the PRV neuroanatomical studies is that manipulations of the VMH were not confined to this nucleus, causing ancillary stimulation or damage to the fibers of passage from the PVN, retrochiasmatic area, and dorsomedial, arcuate, and periventricular nuclei to brainstem and spinal cord sites important for the sympathetic control of adipose and other tissues underlying the metabolic and motivational aspects of ingestive behavior (reviewed in Ref. 151). Thus, we conclude that the VMH is not part of the SNS outflow to the periphery generally (152), or WAT specifically (161, 162) and does not participate in the mobilization of WAT via the sympathetic innervation of this tissue. This is not to suggest, however, that the VMH is not involved in seasonal responses per se; rather, the direct effects of the VMH on body fat and energy metabolism via the SNS are not supported. The VMH does appear to play an important role in reproductive behavior in general and a role in the photoperiodic control of reproductive status specifically. In terms of the latter, lesions of the VMH in Syrian hamsters showing SD-induced gonadal regression trigger accelerated gonadal recrudescence compared with pinealectomized hamsters or sham-operated controls (172). This suggests that an intact VMH is essential for the continued maintenance of SD-induced reproductive inhibition (172). Perhaps the continued stimulation of the neurons within the VMH that possess MEL receptors in Syrian hamsters (47) is necessary for maintenance of SD physiology in these hamsters.

The SNS Is a Possible Mechanism Underlying Photoperiod-Induced Changes in Seasonal Adiposity

Here, we posit a possible mechanism whereby seasonal changes in adiposity may be mediated via alterations in SNS outflow to WAT, BAT, and the adrenal medulla in Siberian hamsters specifically, and perhaps in Syrian hamsters and other animals showing photoperiod/MEL-induced changes in body fat, more generally. We believe that the SCN is especially suited to coordinate seasonal changes because it functions as a biological clock that generates circadian behavioral and physiological rhythms (173), it appears vital for the reception of MEL-encoded photoperiod signals (33, 34, 52, 53), and it is part of the SNS outflow to WAT, BAT (161, 162) and the adrenal medulla (174), as well as sympathetic and parasympathetic connections to a variety of other peripheral tissues (174; reviewed in Ref. 55) as revealed using the PRV tract tracing technique.

In terms of seasonal obesity and involvement of the SNS and SCN, we recently sought to determine if the SCN neurons that are part of the sympathetic outflow to WAT and BAT also express the MEL_{1a} receptor, the functional MEL receptor subtype for seasonal responses. This was accomplished by labeling the sympathetic outflow from brain to WAT (164) and BAT (C-K. Song and T. Bartness, unpublished data) in Siberian hamsters using the PRV as a retrograde trans-synaptic tract tracer injected into IWAT or interscapular BAT combined with labeling of brain MEL_{1a} receptors using *in situ* hybridization. Here, we will discuss the findings for WAT only. The SCN contains the highest number of MEL_{1a} + PRV neurons compared with the other brain areas exhibiting MEL_{1a} receptor gene expression. There are also, however, substantial numbers of MEL_{1a} + PRV colocalized cells in the PVN, zona incerta, and reuniens/xiphoid area of the thalamus, dorsomedial nucleus, and to a lesser degree in the periventricular area fiber system, anterior hypothalamus, perifornical area, and paraventricular nucleus of the thalamus (PVT). Although the role of many of these areas in lipid mobilization (the response seen in SD-housed Siberian hamsters) is unclear or unknown, the SCN has been shown to be involved in increases in lipid mobilization generally (175–177; reviewed in ref. 150), and increases in photoperiod-induced lipid mobilization more specifically (33, 34, 52). For example, coronal microknife cuts just behind the SCN block the increases in lipid mobilization triggered by 24-hr fasts, forced exercise (swimming), cold exposure, and insulin-induced hypoglycemia in laboratory rats (178). Furthermore, microinfusions of SD-like MEL signals into the SCN trigger SD-like responses in Siberian hamsters (54), including decreases in body fat (25). Moreover, SCN lesions block the ability of SD-like exogenous MEL signals to decrease body and fat pad masses in pinealectomized Siberian hamsters (33, 34, 52, 150).

These data, strongly implicating the SCN in the SD-induced changes in body fat, added to what is known about the control of seasonal adiposity and other responses triggered by the changes in the photoperiod/MEL secretion duration, have been summarized graphically in Figure 1 (the number in brackets corresponds to the circled number in Fig. 1). Specifically, for photoperiod-induced body fat decreases in Siberian hamsters, we know the following.

The duration of night [1a] is the critical environmental stimulus triggering a decrease in body fat (i.e., with increasing duration in fall/winter; reviewed in Refs. 5 and 6).

This photic information is received by the retinal ganglion cells of the eye [1b] and transmitted to the SCN [2] via the retinohypothalamic tract and then to the pineal [3] through an identified multisynaptic pathway (16).

At the pineal [3], this photic information is transduced

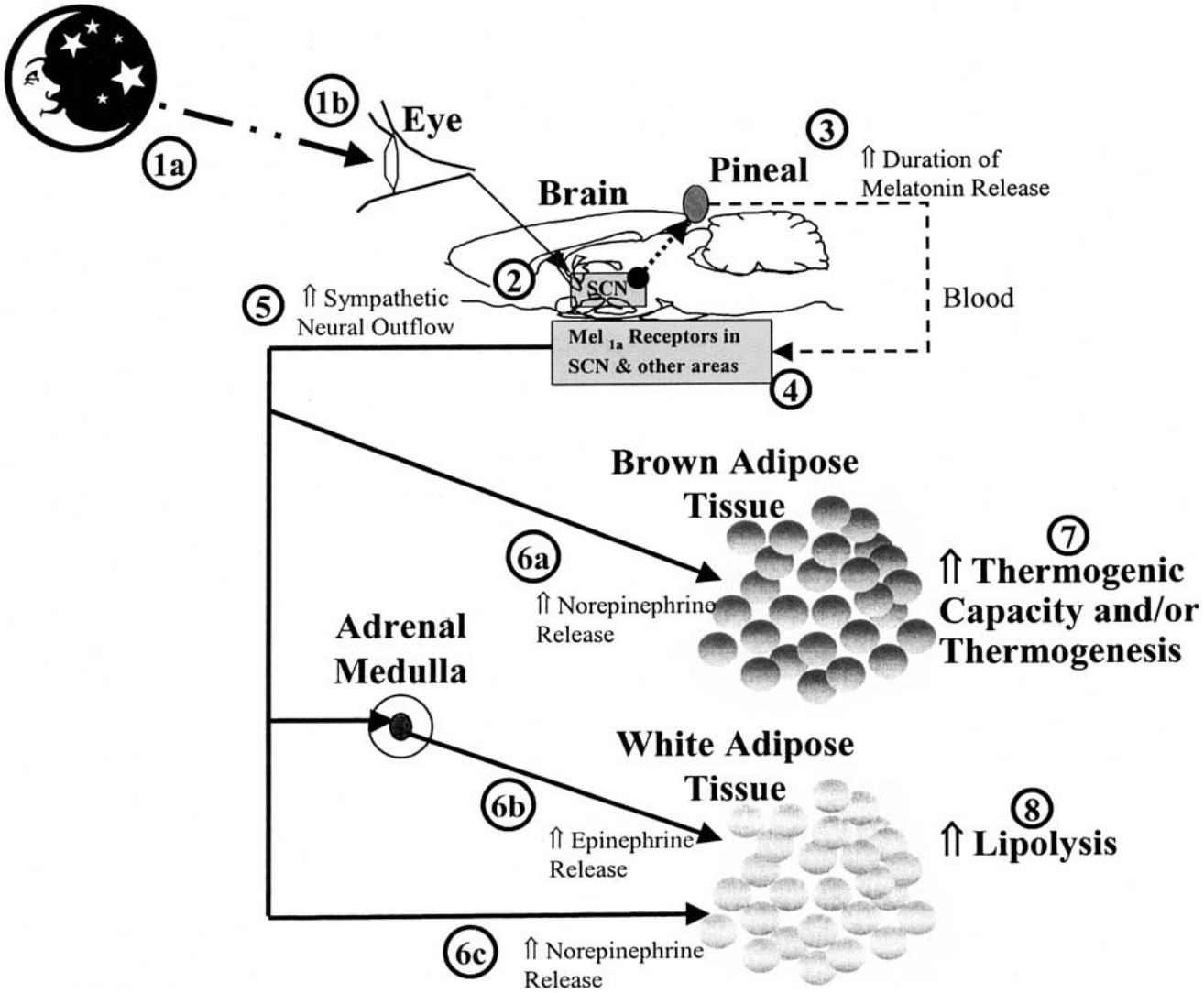

Figure 1. Schematic illustration of the possible mechanism underlying the photoperiod-induced decreases in seasonal adiposity in Siberian hamsters. See text for a description of the system components and explanation for the numbers.

into a biochemical signal through the lengthening of the duration of MEL secretion that is roughly proportional to the lengthening of the dark period (10, 25).

Circulating MEL binds to the functional receptors mediating photoperiodic responses (MEL_{1a} receptors), especially those found on SCN neurons [4], but also elsewhere (51, 179), some of which are part of the CNS origins of the SNS outflow [5] to the periphery (164).

The stimulation of these MEL_{1a} receptors located on SNS outflow neurons by MEL increases the sympathetic drive on several peripheral tissues, including WAT [6a], BAT [6c], and adrenal medulla [6b].

Increases in the sympathetic drive (increased norepinephrine release; 180) via the SNS innervation of BAT [6a] (162, 181) increases BAT thermogenesis, growth, and/or thermogenic capacity [7] (180, 182).

Increases in the sympathetic drive on the adrenal medulla [6b] increases epinephrine release into the circulation, affecting many tissues and promoting lipolysis in WAT [8] (183).

Increases in the sympathetic drive on WAT (156, 161) via its SNS innervation increases norepinephrine release from the nerve endings [6c] (156), also promoting WAT lipolysis [8] (183, 184).

Although the above hypothesized scenario focuses on the SNS outflow from brain to WAT as the primary mechanism underlying seasonal changes in adiposity by SD-housed Siberian hamsters, other factors are involved specifically, surgical (184) or chemical (183) sympathetic denervation of WAT only partially blocks SD-induced body fat decreases in these hamsters. Similarly, removal of only the adrenal medulla, the other branch of the sympathetic outflow, eliminates epinephrine-induced lipolysis, but only partially blocks SD-induced decreases in body fat (183). Sympathetic denervation of WAT combined with adrenal demedullation, however, completely blocks SD-induced

body fat decreases (183). Perhaps the ability of SCN lesions to completely block SD-induced lipid mobilization by Siberian hamsters is due to a centrally induced blockade of sympathetic outflow to both the adrenal medulla and WAT. It is unknown whether there are MEL receptors on neurons comprising the brain-SNS-adrenal medulla circuitry; however, the patterns of infection after PRV injections into the adrenal medulla of rats (171) or Siberian hamsters (M. Bamshad and T. Bartness, unpublished data) are quite similar to those seen after injection of PRV into WAT (161, 163). In addition, it may be that increases in energy expenditure via increased BAT thermogenesis and potential thermogenesis from pockets of ectopically induced brown adipocytes in WAT (185), as well as increased sensitivity to catecholamines in WAT, contribute to the decreases in seasonal adiposity in Siberian hamsters. That is, SD-exposed Siberian hamsters have increases in BAT norepinephrine turnover (180), as well as increases in gene expression for uncoupling protein-1 (UCP-1), one of a family of uncoupling proteins that is primarily responsible for the thermogenic activity of BAT (186), and peroxisome proliferator-activated receptor gamma (PPARγ) coactivator-1 (PGC-1) (134), a critical co-activator of UCP-1 (187). There also may be increased sensitivity to catecholamines by Siberian hamster WAT, based on SD-induced increases in WAT β_3-adrenergic receptor gene expression in these animals (188). Finally, SD-exposed Siberian hamsters also show recruitment of dormant brown adipocytes and/or the induction of transdifferentiation of white adipocytes into brown adipocytes in their retroperitoneal WAT depots, as evidenced by the SD-induced increase in UCP-1 gene expression in this tissue (188). This effect seems identical to that occurring within otherwise similar white adipocyte populations when the sympathetic drive on WAT increases, such as occurs with cold exposure or pharmacological stimulation of β_3-adrenergic receptors, the major postganglionic sympathetic adrenergic receptor of WAT that, when stimulated, promotes lipolysis (185). Taken together, the SD-induced decreased seasonal adiposity of Siberian hamsters, and perhaps other species showing decreases in body fat in SDs, may be promoted by a coordinated suite of changes in WAT and BAT gene transcription that ultimately facilitates lipid mobilization and utilization of lipid fuels largely, but not exclusively (i.e., adrenal medullary catecholamines), due to increases in sympathetic drive to adipose tissues (see discussion in the "Summary" below).

The above speculation seems reasonable as a possible, or even likely, mechanism by which Siberian hamsters and other animals that get thinner in SDs decrease their lipid stores; however, what mechanisms underlie the SD-induced increase in adiposity in species such as Syrian hamsters? A parsimonious view of this phenomenon might be to assume that in Syrian hamsters and other species showing SD-induced body fat increases, MEL inhibits rather than stimulates the SNS drive on WAT. Support for this notion is indirect relative to WAT, but suggestive of an involvement of the SNS. Specifically, SD exposure of Syrian hamsters decreases norepinephrine turnover in heart (189) with a concomitant LD-like norepinephrine turnover in BAT (107, 189, 190), despite increases in BAT mitochondrial content estimated by cytochrome c oxidase activity, and BAT mitochondrial proton conductance estimated by guanosine-5′-diphosphate (GDP) binding to isolated BAT mitochondria (190). In addition, it is possible that SDs reduce the sympathetic drive on WAT as in heart, although it has never been measured to date. This could not only promote lipid accumulation via a decrease in basal lipolysis levels, but also could increase adipocyte proliferation within the WAT pads. That is, decreases in sympathetic drive on WAT seen in many obesity models (191–193) including human obesity (1) is associated with increases in fat cell number (hyperplasia). This effect is most striking with elimination of sympathetic drive via denervation in hamsters (184) as well as rats (194). Indeed, SD-exposed Syrian hamsters have increases in fat cell number in several WAT pads (195). The SD-induced increases in adiposity are not primarily due to increases in food intake because the developing obesity often, but not always, occurs independently of significant overeating (11). Thus, it is possible that SDs decrease the sympathetic drive on WAT in these animals to promote increases in lipid storage while the sympathetic drive on BAT is unchanged, thereby promoting energy savings.

Summary

We have presented data and speculation concerning the control of seasonal obesity by the photoperiod/MEL on its targets, and have primarily focused on the findings from the most commonly studied species showing seasonal changes in adiposity—Siberian and Syrian hamsters. The data to date are not compelling for a direct effect of MEL on WAT and BAT, despite some recent data to the contrary. Thus far, none of the possible hormonal intermediaries for the effects of MEL on seasonal adiposity appear likely as a mechanism by which MEL affects the photoperiodic control of body fat levels indirectly. One possible hormonal candidate that seems to deserve more study is glucagon. We also provided evidence pointing toward the SNS as a likely mediator of the effects of MEL on SD-induced body fat decreases in Siberian hamsters through increases in sympathetic drive on WAT and BAT, and we speculated that decreases in the SNS drive to adipose tissues may underlie the photoperiod-induced seasonal increases in adiposity of species such as Syrian hamsters. Clearly, we need to deepen our understanding of seasonal adiposity, although, to our knowledge, this is the only environmentally induced change in body fat where the key elements of its external trigger have been identified and can be traced to and through their transduction into a physiological stimulus that ultimately affects identified responses of white adipocyte physiology and cellularity (164 and Fig. 1 with associated text above). Finally, the comparative physiological approach to the study of sea-

sonal adiposity seems highly likely to yield significant insights into the mechanisms underlying this phenomenon and was the guiding stimulus for the our explorations into the SNS innervation of WAT.

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