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Modulation of leptin sensitivity by short photoperiod acclimation in the Djungarian hamster, *Phodopus sungorus*

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Abstract During seasonal acclimation, Djungarian hamsters spontaneously exhibit a reduction in food intake, body mass and body fat stores, which is externally cued by shortening of day length in autumn and controlled by a sliding set-point. We investigated the function of the leptin adipostatic feedback system in the photoperiodic control of seasonal acclimation. In response to mouse recombinant leptin injections for 10 days, long day photoperiod (LD) and short day photoperiod (SD)-acclimated hamsters decreased food intake and body mass. The reduction of body mass was due to the depletion of body fat, as revealed by carcass composition analysis. In SD hamsters, leptin caused a larger reduction of body fat mass than observed under LD conditions, whereas the anorectic effect was similar in both photoperiods. The serum leptin concentration was 9.3 ± 1.2 ng/ml in LD-acclimated hamsters and decreased significantly to 4.2 ± 0.8 ng/ml and 2.1 ± 0.6 ng/ml in hamsters exposed to SD for 66 days and 116 days, respectively ($P < 0.001$). A strong positive correlation between total body fat mass and serum leptin concentration was found ($r_S = 0.935$, $P < 0.0001$, $n = 70$). Despite the anorectic action of exogenous leptin, higher endogenous leptin levels in LD hamsters were paralleled by higher food intake in LD hamsters as compared to SD hamsters. This paradoxical finding further supports the increased leptin sensitivity in SD hamsters as judged from leptin treatment experiments. We tested the functional significance of leptin for the controlled down-regulation of food intake and body mass induced by short photoperiod. Food restriction for 10 days during the transition phase decreased body mass below the desired sliding set-point, which was recovered in control hamsters following ad libitum refeeding. Treatment with mouse recombinant leptin during ad libitum refeeding inhibited the recovery of body mass and blunted the increase of food intake observed in controls, indicating that the sliding set-point utilizes leptin as a signal for the adjustment of the appropriate body mass level.

Key words Body weight · Melatonin · Sliding set-point · Adipose tissue · Energy expenditure

Abbreviations *body mass$_{evisc}$* eviscerated body mass · *LD* long day photoperiod · *SD* short day photoperiod

Introduction

Seasonal cycles of food intake and body mass are well characterized in several mammalian and avian species and are utilized as animal models to study the physiological and molecular basis of energy metabolism regulation (Steinlechner and Heldmaier 1982; Zucker and Boshes 1982; Dark et al. 1983; Heldmaier 1989; Bairlein and Gwinner 1994: Mauer and Bartness 1994; Körtner and Heldmaier 1995; Klingenspor et al. 1996; Boyer et al. 1997; Mercer 1998). A common feature of these cycles is that seasonally appropriate food intake and body mass appear to be governed by a sliding set-point, which is modulated by environmental cues and/or endogenous circannual rhythms (Steinlechner et al. 1983; Dark and Zucker 1984). These systems could be superior to other frequently studied animal models as the alteration of the set-point can occur in either direction, is observable in genetically wildtype animals (not due to a genetic defect), does not invoke manipulation of food quality or quantity or other environmental constraints, and most importantly, is completely reversible.

The Djungarian hamster (*Phodopus sungorus*) represents such a seasonal animal model, which is employed

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to increase our understanding of the set-point mechanisms regulating energy homeostasis in mammals. In contrast to circannual prehibernation fattening in hibernators, the annual body mass cycle of the Djungarian hamster is exogenously cued by photoperiod (Steinlechner and Heldmaier 1982). Hamsters bred and raised in summer-like long day lengths (LD) have a mean body mass of >40 g, which is largely due to a high body fat level (Bartness and Goldman 1988). In response to winter-like short day lengths (SD) this hamster species, despite the presence of ad libitum food supply, spontaneously reduces food intake and body mass and thereby decreases total energy expenditure by approximately 40% (Heldmaier 1989). In concert, an array of physiological and morphological winter adaptations occur involving gonadal regression, growth of white winter fur, occurrence of daily torpor, decreased total resting metabolic rate, increased thermogenic capacity and improved cold resistance (Hoffmann 1973; Heldmaier and Steinlechner 1981; Heldmaier et al. 1981). The physiological winter condition is maintained for 3 months, after which hamsters become refractory to SD and increase body mass again. The SD-mediated decrease of body mass is largely generated by depletion of lipids stored in white and also brown adipose tissue. At any time of the body mass cycle, hamsters 'know' the appropriate body fat content as demonstrated by fasting-refeeding (Steinlechner et al. 1983) and lipectomy experiments (Mauer and Bartness 1994).

The photoperiodic response is mediated by the action of the pineal hormone melatonin acting through its receptor located in the hypothalamus. Even though the transition from the fat to the lean state can be induced by melatonin injections or timed infusions of melatonin (Holtorf et al. 1985; Bartness et al. 1993), it is not understood how the neuroendocrine mechanism of photoperiodic time measurement can induce the regulated decrease of the sliding set-point of food intake and body mass. One prerequisite for controlled down-regulation of body mass and body fat content in response to SD is the ability to perceive the amount of fat deposited in the body. Leptin and the leptin receptor, as key components of an adipostatic feedback mechanism in mammals (Zhang et al. 1994; Tartaglia et al. 1995), are very likely to be involved in seasonal control of body fat deposition. The blood serum level of leptin, a cytokine mainly expressed and secreted by adipocytes, reflects body fat mass (Considine et al. 1996). In mice, peripheral and central administration of recombinant leptin decreases food intake and body fat (Halaas et al. 1997), most likely exerting its effects via leptin receptors expressed in the brain. Natural mutations of the leptin gene (Lep^{ob}) and the leptin receptor gene ($Lepr^{db}$) cause imbalanced energy metabolism and obesity (for review see Considine and Caro 1997; Friedman and Halaas 1998).

In arctic ground squirrels, the growth of fat mass during seasonal prehibernation fattening is not reflected by an increase of serum leptin levels (Boyer et al. 1997). However, leptin treatment during the early and also the late phase of prehibernation fattening both decreased food intake and body weight gain (Ormseth et al. 1996; Boyer et al. 1997). In addition to the anorectic action, leptin also appeared to lower food efficiency in ground squirrels.

In the Djungarian hamster, leptin mRNA levels in adipose tissue are altered according to the seasonal change of body fatness, showing maximal levels in fat hamsters housed in summer-like LD (Klingenspor et al. 1996). Thus, high leptin expression levels coincide with peak levels of food intake and body mass challenging the putative function of leptin as a satiety signal in the Djungarian hamster. In the present study, the functional role of the leptin adipostatic feedback mechanism in the photoperiodic control of body mass was investigated in this animal model. In hamsters acclimated to LD and SD the serum leptin concentration and the effect of recombinant mouse leptin on food intake, body mass and carcass composition were compared. We also investigated whether exogenous leptin can perturb the adjustment of appropriate body mass during SD-induced down-regulation of the set-point.

Materials and methods

Djungarian hamsters (*P. sungorus*) were bred and raised at our institute in LD (16 h light:8 h darkness, lights on at 4:00 a.m.) and room temperature. Hamsters were weaned at the age of 3 weeks and caged separately after 4 weeks. They received hamster breeding chow diet (Altromin 7014) and water ad libitum. Hamsters were kept at 23 ± 1.5 °C ambient temperature throughout all experiments. Males and females were studied at an age of 4–8 months. Body weight and food intake were continuously monitored in all experiments to 0.1 g. Food intake was measured by daily weighing of food hoppers, carefully checking cages for food spillage. Chow was stored in the animal room. A constant humidity of 50% was maintained in the animal room; no change in the water content of food could thus occur.

We compared the effect of leptin treatment on body mass, food intake, carcass composition, and serum leptin concentration in ad libitum-fed hamsters either maintained in LD (25 males, 12 females) or acclimated to SD (10 h light:14 h darkness, lights on at 8:00 a.m.) for 56 days (12 males and 12 females). Hamsters were injected subcutaneously twice daily (at 8:00 a.m. and 5:00 p.m.) with mouse recombinant leptin dissolved in phosphate-buffered saline (6.5 $\mu g\ g^{-1}\ day^{-1}$, supplied by Amgen, Thousand Oaks, Calif.) for 10 days, whereas controls received saline (0.9% NaCl). During a 7-day pretreatment period all hamsters received subcutaneous injections of saline in order to eliminate arousal effects. A further group of hamsters (4 males, 7 females) not treated with leptin was kept in SD for 106 days in order to investigate the fully expressed SD response. Leptin-treated and control hamsters were killed on day 11 after onset of treatment between 9:00 a.m. and 11:00 a.m. in CO_2-anesthesia by puncture of the posterior vena cava. The last leptin injection was given at 5:00 p.m. on day 10. Blood serum was sampled and stored at −70 °C until assay of serum leptin concentration. Defined tissue depots (inguinal white adipose and axillary brown adipose tissue, hindleg femoral skeletal muscle) were dissected and weighed.

Serum leptin concentrations were determined in a solid phase sandwich enzyme immunoassay using affinity purified rabbit anti-recombinant murine leptin immobilized in microtiter wells. Bound leptin was detected with affinity purified anti-murine polyclonal antibody conjugated to horseradish peroxidase, and quantitated with a chromogenic substrate (TMB). Leptin concentrations were

calculated from standard curves generated for each microtiter plate using recombinant murine leptin. The limits of detection for the assay were 0.15 ng/ml and the intra- and inter-assay coefficients of variation were 4.5% and 8%, respectively, determined from internal murine leptin controls. Due to the heterologous leptin standard, the measured serum leptin concentrations are relative but not necessarily absolute. The serum samples were always assayed at three dilutions, in duplicate, with two dilutions normally falling into the range of the standard curve. The comparison of calculated concentrations of the two dilutions from each hamster demonstrated that the values vary from each other no more than 13%.

For carcass composition analysis the cheek pouches were emptied and the entire gastrointestinal tract (excluding adhering omental fat) was removed. The eviscerated carcass was dried to constant weight at 60 °C for determination of body water content. Total body fat was extracted from the dried carcass by chloroform extraction in a Soxhlet apparatus.

We also investigated whether leptin treatment could alter the seasonal program of body mass control cued by SD. Hamsters ($n = 20$; 10 males, 10 females) were acclimated to SD (10 h light: 14 h darkness, lights on at 8:00 a.m.) for 64 days, subjected to 14 days of food restriction (60% of ad libitum food intake), and refed ad libitum afterwards. With the onset of ad libitum refeeding, half of the hamsters ($n = 10$, balanced for sex) were injected subcutaneously with mouse recombinant leptin for 10 days as described above, whereas the control group received saline. After termination of treatment recording of body mass and food intake was continued for 3 weeks.

Simple linear regression analysis was performed to determine the contribution of body fat and fat-free mass to the SD-mediated change of body mass. For analysis of the correlation of serum leptin concentration and body fat mass, the Spearman rank correlation coefficient r_S was calculated. Multivariate analysis of variance (MANOVA) was employed to test the effect of photoperiod, leptin treatment and sex on body mass and food intake. ANOVA served to compare groups at the end of treatment. Fat mass, fat-free mass and serum leptin concentration data were log-transformed prior to statistical analysis, in order to prevent deviation from normal distribution (Kolmogorov-Smirnov). For these variables ANCOVA adjusting for either fat mass or body mass on the day before onset of leptin treatment was performed. Data are expressed as mean values ± SEM. Statistical procedures were performed using SPSS 8.

Results

We compared the effect of mouse recombinant leptin treatment in hamsters acclimated to LD and SD. In response to leptin treatment, LD hamsters and SD hamsters decreased in body mass as compared to saline-injected controls (Fig. 1). The mean absolute body mass decrease after 10 days treatment was 1.7 g in LD hamsters and 1.6 g in SD hamsters, as compared to controls. This decrease represents −4.4% and −5.5% of control body mass under LD and SD conditions, respectively.

The control level of cumulative food intake was 26.0 ± 1.0 g/10 days in LD hamsters as compared to 21.1 ± 0.4 g/10 days in SD hamsters (66 days in SD) (ANOVA, $P < 0.001$). Food intake was not decreased further in hamsters acclimated to SD for 116 days (22.1 ± 0.9 g/10 days). During the pretreatment period mean cumulative food intake was identical in control and leptin-treated hamsters in either photoperiod (data not shown). Subsequent leptin treatment for 10 days decreased cumulative food intake (Fig. 2). As compared to controls, hamsters treated with leptin consumed

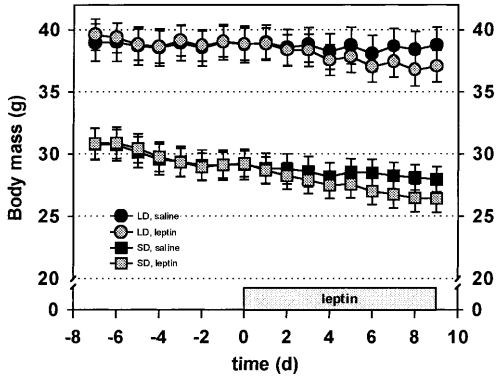

Fig. 1 Effect of two daily leptin injections (6.5 μg/g per day) for 10 days on body mass in hamsters kept in long photoperiod (LD) and hamsters transferred to short photoperiod (SD) 56 days prior to treatment. MANOVA was employed to test the effect of photoperiod ($P < 0.001$), leptin ($P < 0.05$), and sex ($P < 0.01$) on body mass. Data are presented as mean values ± SEM ($n = 18$–19 for each LD treatment groups; $n = 12$ for SD treatment groups)

3.5 ± 1.5 g/10 days and 3.1 ± 0.7 g/10 days less food in LD and SD, respectively. Thus, the anorectic effect of leptin is similar in LD and SD hamsters. The decreased food intake level represents 86% of the corresponding control level in both photoperiods.

Carcass composition analysis was employed to investigate the effect of leptin treatment on body fat mass in LD and SD hamsters. Carcass composition data obtained from control hamsters acclimated to LD and SD verified that the SD-mediated decrease of body mass is equally due to a reduction of fat mass [fat mass (g) $= -6.56 + 0.48 \times$ body $\text{mass}_{\text{evisc}}$ (g), $r = 0.911$, $P < 0.001$, $n = 39$] and fat-free mass [fat-free mass (g) $= -6.59 + 0.52 \times$ body $\text{mass}_{\text{evisc}}$ (g), $r = 0.920$, $P < 0.001$, $n = 39$], where body $\text{mass}_{\text{evisc}}$ is eviscerated body mass. Leptin treatment caused a reduction of body fat mass and the mass of adipose tissue depots (Table 1). As compared to controls, leptin-induced reduction of body

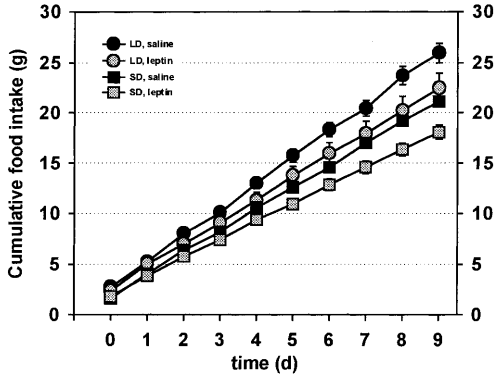

Fig. 2 Effect of two daily leptin injections (6.5 μg/g per day) for 10 days on cumulative food intake in hamsters kept in LD or exposed to SD for 56 days prior to treatment. MANOVA was employed to test the effect of photoperiod ($P < 0.001$), leptin ($P < 0.01$), and sex ($P < 0.05$) on body mass. Data are presented as mean values ± SEM ($n = 18$–19 for each LD treatment groups; $n = 12$ for SD treatment groups)

Table 1 Serum leptin concentration, carcass composition, adipose tissue and skeletal muscle mass (mean ± SEM) of Djungarian hamsters treated with leptin or saline for 10 days in long photoperiod (LD) and in short photoperiod (SD) conditions. One hamster with a serum leptin concentration of 51 ng/ml was excluded from the analysis. Prior to analysis of carcass composition, the gastrointestinal tract and defined adipose/skeletal muscle depots were sampled. Thus the total body-fat mass is underestimated. (*BAT* brown adipose tissue, *WAT* white adipose tissue)

Treatment	Photoperiod			
	LD		SD 66 days	
	Saline	Leptin	Saline	Leptin
Leptin (ng/ml)	9.3 ± 1.2	6.9 ± 1.0	4.2 ± 0.8	2.2 ± 0.5
Fat free mass (g)	23.1 ± 0.9	23.5 ± 0.8	18.8 ± 0.6	19.4 ± 0.5
Fat mass (g)	9.2 ± 0.6	7.9 ± 0.6	4.5 ± 0.5	2.8 ± 0.6
WAT (g)	1.38 ± 0.12	1.2 ± 0.10	0.76 ± 0.10	0.47 ± 0.12
BAT (g)	0.70 ± 0.06	0.57 ± 0.05	0.61 ± 0.05	0.44 ± 0.03
Muscle (g)	0.21 ± 0.01	0.22 ± 0.01	0.17 ± 0.01	0.16 ± 0.01
n	18	19	12	12

fat mass was 1.3 g in LD hamsters and 1.7 g in SD hamsters. The comparison of the effect of leptin on body fat mass in LD and SD is complicated by the fact that body fat mass of individual hamsters prior to the onset of treatment is not known and depends on body mass of hamsters. Therefore we employed ANCOVA of body fat mass adjusting for body mass on the day before the start of treatment. Both short photoperiod and leptin treatment significantly reduced body fat mass (Table 2); males also had a higher body fat mass than females. Interestingly, we detected a significant interaction of photoperiod and leptin. This result indicates that the effect of leptin on body fat mass is more pronounced in SD hamsters. Fat-free mass was not affected by leptin treatment (Tables 1, 2).

The serum leptin concentration was 9.3 ± 1.2 ng/ml in LD hamsters and decreased significantly to 4.2 ± 0.8 ng/ml and 2.1 ± 0.6 ng/ml in hamsters exposed to SD for 66 days and 116 days, respectively (ANOVA, $P < 0.001$). Serum leptin concentration was strongly correlated with body fat mass and to a lesser degree with eviscerated body mass (Fig. 3). Serum leptin concentration in leptin-treated hamsters was decreased as compared to controls (Table 1). ANCOVA of serum leptin data adjusting for body fat mass demonstrates that the decrease in serum leptin in response to leptin treatment and short photoperiod corresponded to the depletion of body fat mass (Table 2).

We also investigated whether the seasonal adjustment of body mass and food intake in SD hamsters according to the sliding set-point could be impaired by mouse recombinant leptin treatment. Hamsters transferred to SD decreased body mass continuously (Fig. 4, upper graph). After 64 days exposure to SD, hamsters were subjected to food restriction for 2 weeks resulting in a decrease of body mass by approximately 6–7 g below the expected level in ad libitum-fed hamsters. A more than two-fold increase of food intake occurred on the 1st day of refeeding in all hamsters, but during the remaining 9 days of treatment daily food intake was lower in hamsters treated with leptin (Fig. 4, lower graph). Cumulative food intake of leptin-treated hamsters was 23.9 ± 1.5 g/10 days as compared to 27.3 ± 1.8 g/10 days in controls. Accordingly, in control hamsters body mass returned to the seasonally appropriate level within 10 days, whereas this response was completely inhibited in hamsters treated with leptin. The latter started to gain body mass when leptin treatment was terminated after 10 days (Fig. 4, upper graph). In both control and leptin-treated hamsters, gain of body mass ceased as the appropriate body mass according to the sliding set-point was accomplished, and then began to decrease further. Therefore, temporary leptin treatment had no apparent long-term effects on the set-point of food intake and body mass.

Discussion

In order to directly examine possible seasonal modulation of leptin sensitivity, the leptin response was

Table 2 ANCOVA was employed to test the effect of photoperiod (PP), leptin (L) and sex (S) on fat mass, fat-free mass and serum leptin concentration. Body mass on the day before treatment (fat mass, fat-free mass) and fat mass (serum leptin concentration) were employed as covariates. Data were log transformed [$\log_{(X+1)}$] prior to ANCOVA

Source	Fat mass			Fat-free mass			Leptin		
	SS	*df*	*P*	SS	*df*	*P*	SS	*df*	*P*
PP	0.100	1	**	1.0×10^{-5}	1	NS	0.049	1	NS
L	0.214	1	***	1.5×10^{-3}	1	NS	2.1×10^{-5}	1	NS
Sex	0.069	1	**	0.026	1	***	0.035	1	NS
PP*L	0.039	1	*	2.1×10^{-4}	1	NS	0.019	1	NS

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

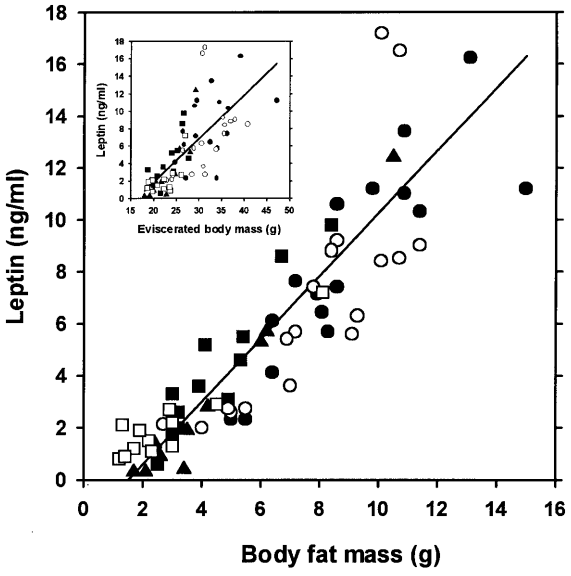

Fig. 3 Correlation of serum leptin concentration with body fat mass ($r_S = 0.935$, $P < 0.0001$, $n = 70$) and eviscerated body mass (*inset*, $r_S = 0.813$, $P < 0.0001$, $n = 70$) in control (*black symbols*) and leptin-treated (*open symbols*) hamsters exposed to LD (*circles*) and SD (*squares*: 66 days SD, *triangles*: 116 days)

compared in LD hamsters and SD hamsters. In both physiological states, injection of mouse recombinant leptin for 10 days caused a decrease of body mass below the level of saline-injected controls. The relative effect of leptin injections on body mass was comparable to results obtained with leptin injections in wild-type mice (Halaas et al. 1995; Pelleymounter et al. 1995).

Body fat mass was assessed by carcass composition analysis. For controls, body fat mass in SD hamsters was 50% lower than in LD hamsters (Table 1). However, in response to leptin treatment SD hamsters lost significantly more body fat mass (Table 2). When body fat depletion in response to leptin was expressed as a percentage of the corresponding control, body fat mass was decreased by 37% in SD hamsters as compared to 14% in LD hamsters (Table 1). Our results provide the first evidence that short photoperiod exposure increases leptin sensitivity in the Djungarian hamster.

The role of leptin in the control of the seasonal body mass cycle was further evaluated by measuring the leptin concentration in hamster serum. The serum leptin concentrations obtained with the applied assay system are well in the range measured in wildtype mice (Ahima et al. 1996; Kamohara et al. 1997), ground squirrels (Boyer et al. 1997) and humans (Considine et al. 1996). Serum leptin concentration was elevated greater than four-fold in LD hamsters as compared to hamsters acclimated to SD for 116 days. This is consistent with our previous finding that leptin mRNA levels in white and brown adipose tissue are increased in hamsters exposed to LD (Klingenspor et al. 1996) and confirms the role of leptin gene transcription and/or mRNA stability in adipose tissue for the seasonal adjustment of circulating leptin levels in the Djungarian hamster.

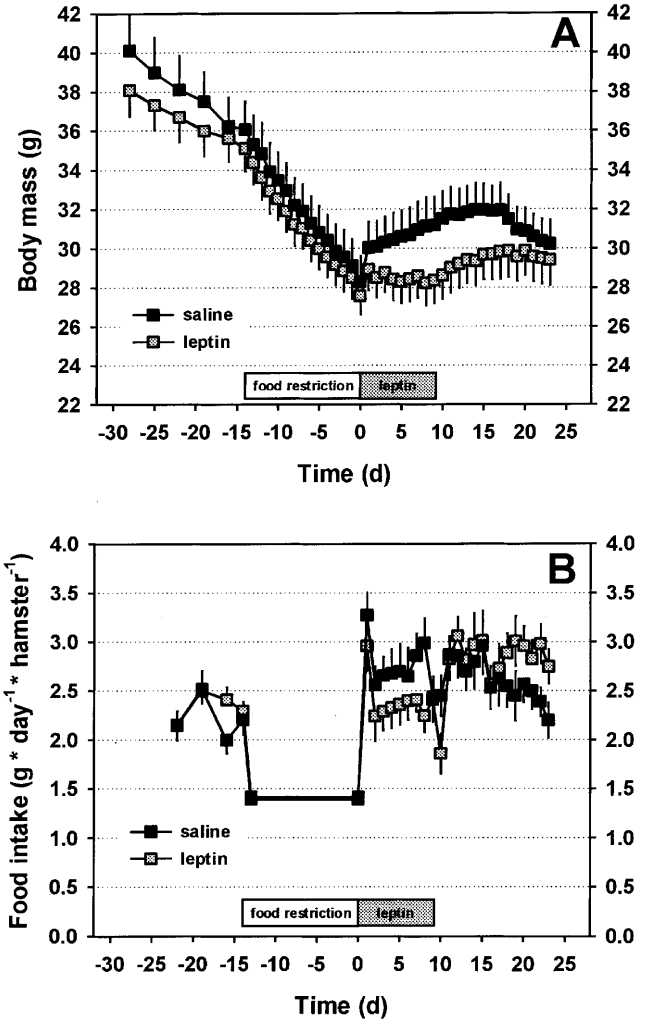

Fig. 4 Effect of leptin treatment on body weight (*upper graph*) and food intake (*lower graph*) during refeeding. After 64 days, SD-acclimated hamsters were food-restricted (60% of ad libitum) for 2 weeks and refed afterwards. During 10 days of ad libitum refeeding hamsters received two daily leptin injections (6.5 μg/g per day). Controls received saline. Data are presented as mean values ± SEM ($n = 10$ for treatment groups)

Serum leptin concentration in leptin-treated hamsters was lower when compared to the controls (Table 1). In our study, blood was sampled for leptin measurements more than 16 h after the final leptin injection. Preliminary injection studies in our laboratory indicated that leptin given at the dose used in the experiments should be turned over within this time span (results not shown). Therefore it is most likely that the serum concentration assayed in this study represents the endogenous hamster leptin level. This level is reduced as expected from the decrease in body fat mass in response to the treatment (Tables 1, 2).

A significant positive correlation between body fat mass and serum leptin concentration was found, demonstrating that serum leptin reflects the seasonal change of fat mass deposited in adipose tissue. This situation resembles the observation made in humans where a

positive correlation between body fat and leptin concentration was determined in normal and obese subjects suggesting the development of leptin resistance in human obesity (Considine et al. 1996). In the present study, leptin treatment of Djungarian hamsters clearly decreased body fat mass and food intake. Thus, due to the anorectic action of leptin the greater-than-four-fold elevated serum leptin level observed in LD hamsters should result in lower food intake. Paradoxically, food intake is actually higher in LD hamsters as compared to SD hamsters, suggesting a reduced anorectic potency of leptin in LD hamsters. Surprisingly, the effect of leptin treatment on food intake was similar under LD and SD conditions.

Food intake was inhibited by leptin treatment in both LD and SD hamsters. By comparing food intake and carcass composition data (including excised adipose tissue mass, see Table 1, [1]we estimated whether the observed anorectic effect of leptin could account for the depletion of body fat. For this calculation an energy-assimilation coefficient of 83% was applied (Weiner 1987). During the 10-day leptin-treatment period, LD hamsters assimilated 53 kJ (18.4 kJ/g chow) less energy as compared to controls. This closely corresponds to the 61 kJ energy content of the depleted fat mass (assuming 39 kJ/g fat). Energy intake of leptin-treated SD hamsters was reduced by 47 kJ, whereas energy content of depleted body fat was 80 kJ. Thus, SD hamsters combusted almost twice the amount of fat during the treatment period than could be expected from the reduction of energy intake in response to leptin. This discrepancy could either be due to a reduction of energy assimilation rate or increased energy expenditure in response to leptin. Leptin has been shown to prevent a decrease of metabolic rate and expression of uncoupling proteins in brown fat in response to food restriction (Cusin et al. 1998; Döring et al. 1998). Previous studies have demonstrated that total resting metabolic rate and body temperature of Djungarian hamsters are reduced by SD exposure (Heldmaier 1989). Although our results indicate that these metabolic adaptations may be reverted by leptin treatment in SD hamsters, measurements of metabolic rate and body temperature are necessary to test this hypothesis.

We finally investigated the functional significance of leptin for the controlled down-regulation of food intake and body mass in SD-exposed hamsters. By employment of a food restriction-refeeding experiment, the gradual decline of food intake and body mass induced by SD exposure was manipulated. Treatment with mouse recombinant leptin during refeeding attenuated the adjustment of seasonal-appropriate body mass and food intake. In the post-treatment period food intake and body mass recovered to the seasonally appropriate level. This result provides the first evidence that leptin may be required in the seasonal cycle of body weight as a peripheral signal for the adjustment of energy metabolism to the sliding set-point.

The neuroendocrine pathways mediating leptin signaling are only partially understood and, more significantly, it is not clear how anorectic and metabolic effects of leptin are dissociated in the brain. The altered leptin sensitivity observed in this study resembles observations in polygenic mouse obesity models and human obesity. Currently considered putative mechanisms responsible for altered leptin sensitivity include saturation of leptin transport into the brain, defect or down-regulation of the hypothalamic long form of the leptin receptor and modulation of leptin-signaling pathways downstream of the receptor. In the Djungarian hamster, the effect of short photoperiod on downstream leptin-signaling pathways has been addressed in previous studies. This species is very sensitive to the stimulatory effect of intracerebroventricular NPY on food intake (Boss-Williams and Bartness 1996). Anorectic effects of leptin are partially transmitted through NPY by down-regulation of hypothalamic preproNPY mRNA levels (Erickson et al. 1996; Schwartz et al. 1996), but the orexigenic potency of NPY in the Djungarian hamster is not affected by SD exposure (Boss-Williams and Bartness 1996). In a closely related species (*Phodopus campbelli*), the fasting response of hypothalamic preproNPY mRNA level does not appear to be altered by SD exposure (Mercer et al. 1995). On the other hand, SD acclimation of Djungarian hamsters results in increased sensitivity towards peripherally injected satiety peptides such as bombesin and CCK-8 (Bartness et al. 1986). A parallel may also be drawn to the mechanisms involved in photoperiodic regulation of reproduction. For more than 20 years it has been known that the feedback inhibition of gonadotropin secretion by steroids exhibits increased sensitivity when hamsters are exposed to SD (Ellis and Turek 1979). Interestingly, several recent findings indicate that leptin functions as a regulator of the hypothalamic-pituitary-gonadal axis (Cunningham et al. 1999).

The mechanisms of seasonal modulation of leptin sensitivity remain to be resolved. As leptin has previously been suggested to be a starvation signal, seasonal tuning of leptin sensitivity may increase the odds of survival in winter when food resources and internal energy (fat) stores are minimal.

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