Social defeat increases food intake, body mass, and adiposity in Syrian hamsters

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Foster, Michelle T., Matia B. Solomon, Kim L. Huhman, and Timothy J. Bartness. Social defeat increases food intake, body mass, and adiposity in Syrian hamsters. Am J Physiol Regul Integr Comp Physiol 290: R1284–R1293, 2006. First published December 22, 2005; doi:10.1152/ajpregu.00437.2005.—Overeating and increases in body and fat mass are the most common responses to day-to-day stress in humans, whereas stressed laboratory rats and mice respond oppositely. Group housing of Syrian hamsters increases body mass, adiposity, and food intake, perhaps due to social confrontation-induced stress. In experiment 1 we asked, Does repeated social defeat increase food intake, body mass, and white adipose tissue (WAT) mass in Syrian hamsters? Male hamsters subjected to the resident-intruder social interaction model and defeated intermittently 15 times over 34 days for 7-min sessions significantly increased their food intake, body mass, and most WAT masses compared with nondefeated controls. Defeat significantly increased terminal adrenal noradrenaline and epinephrine, but not epinephrine, content. In experiment 2 we asked, Are 15 intermittent resident-intruder interactions necessary to increase body mass and food intake? Body mass and food intake of subordinate hamsters defeated only once were similar to those of nondefeated controls, but four or eight defeats similarly and significantly increased these responses. In experiment 3 we asked, Do intermittent defeats increase adiposity and food intake more than consecutive defeats? Four intermittent or consecutive defeats similarly and significantly increased food intake and body mass compared with nondefeated controls, but only intermittent defeats significantly increased all WAT masses. Consecutive defeats significantly increased mesenteric and inguinal WAT masses. Plasma leptin, but not insulin, concentrations were similarly and significantly increased compared with nondefeated controls. Collectively, social defeat, a natural stressor, significantly increased food intake, body mass, and adiposity in Syrian hamsters and may prove useful in determining mechanisms underlying human stress-induced obesity.

the response of human and nonhuman animals to various stressors in their environment can involve marked changes in their energy balance. For example, a large segment of humans respond to day-to-day environmental stressors by increasing their food intake, often leading to increases in obesity (13, 36). This stress-induced increase in body and lipid mass may be one of the factors contributing to the rising incidence of obesity with its consequent increased health risks of type II diabetes, high blood pressure, heart disease, some cancers, and compromised immune responses (e.g., Refs. 37, 38). More significant traumatic environmental stressors (e.g., loss of a spouse) can have opposite effects in humans, decreasing food intake and adiposity (7). The typical response of laboratory rats and mice to a wide range of stressors [e.g., swim stress, restraint, handling, immobilization, foot shock, social stress (social defeat)] is to decrease food intake and adiposity. For example, male laboratory rats exposed to intermittent stressors of differing intensities, such as handling and immobilization, decrease their food intake (22). In addition, laboratory rats and mice subjected to restraint stress decrease food intake temporarily but have persisting decreases in body and fat mass for weeks after the restraint sessions end (e.g., Ref. 15). Similar decreases in body mass and food intake also are seen in subordinate male rats exposed to multiple defeats in a social stress situation (24). Subordinate mice also decrease body mass when exposed to multiple bouts of social stress in the resident-intruder paradigm or to continuous housing opposite a dominant, larger conspecific (18). To date, there only is one stress procedure in laboratory rodents where body mass increases after exposure to the stressor, as it typically does in nontraumatically stressed humans (2). Specifically, social dominance is established through physical interactions when a same-size intruder mouse is placed in the home cage of a resident mouse for 10 min and then a perforated barrier is inserted to separate the two mice (allowing for all but tactile sensory stimulation). On the subsequent 21 days, the barrier is removed at an unpredictable time for 10-min physical contact sessions. This procedure triggers significant increases in body mass of the subordinate mice, but it is not accompanied by increases in food intake compared with their dominant counterparts and unpaired/unstressed controls (2).

There is another, apparently unintended, model of stress-induced obesity in a different rodent species. When Syrian (Mesocricetus auratus) or Siberian (Phodopus sungorus) hamsters are group housed, some investigators report a nonsignificant increase in food intake (4, 25) and some a significant increase in food intake (10), but all report significant increases in body and fat mass (1, 4, 10, 25). Group housing of rodents, in general, is a complex environmental condition that can affect a wide range of physiological systems, many of which have been established as factors that impact energy balance such as reproductive system inhibition (e.g., Refs. 3, 39) and decreases in thermal requirements (4). More specifically, the chronic social stress of group housing triggers conflicts resulting in copulatory behavioral disorders (39) and decreases in testes mass and testosterone concentration (3) in subordinates. Thermogenic demands decrease with group housing because of the close quarters with multiple heat sources that consequently reduce thermal energy expenditure, the energy savings of which can promote body and lipid mass gains (4). Group housing, or merely the situation of multiple animals eating together, also promotes increases in food intake via the so-

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called “social facilitation of feeding” across many diverse species such as cows (29), chickens (41), and humans (6). By contrast, there also are effects of group housing that could mitigate increases in food intake or adiposity, including activity-induced increases in energy expenditure due to social interactions as seen in gilts (11) or laboratory rats (26). When the normally solitary-living Syrian hamster is forced into a group housing condition, body and fat mass increase (26), suggesting that the adiposity-encouraging effects of group housing (e.g., thermogenesis savings, social facilitation of feeding) override its adiposity-discouraging effects (e.g., increased exercise, increased stress) and/or alternatively that social stress promotes increases in body and fat mass in this species, an effect opposite that observed in most species (see above).

The social interaction model is the best known test for social stress, and one version of this model is the resident-intruder model (32). In the resident-intruder model, one hamster (the intruder) is placed into the home cage of its opponent (the resident). Dominance in hamsters, in general, and in this paradigm, specifically, is rapidly achieved during the first encounter (20). Social defeat in laboratory rats and mice has wide-ranging effects on physiology and behavior, including suppression of immune function (37, 38), inhibition of reproductive function (39), alterations in hypothalamic pituitary axis (31), and, most relevant in the present study, decreases in food intake and body mass (24). Although social defeat in Syrian hamsters also has been shown to suppress immune function (17) and activate the hypothalamic pituitary axis (e.g., Ref. 16), effects on food intake and body and fat mass have not been studied. Therefore, the purpose of the present study was to test the effects of social defeat on food intake, body mass, fat mass, and some measures of reproductive status and stress in Syrian hamsters. This was accomplished by subjecting adult male Syrian hamsters to the resident-intruder model of social stress for several days. In experiment 1 we asked, Does repeated social defeat increase food intake, body mass, and white adipose tissue (WAT) mass in male Syrian hamsters? Because repeated defeats in these hamsters increased food intake and body and lipid mass, in experiment 2 we asked, Are repeated resident-intruder interactions necessary to increase body mass and food intake; and in experiment 3 we asked, Do intermittent defeats increase adiposity and food intake more than consecutive defeats?

**METHODS**

**Animals and Housing**

Adult male Syrian hamsters (Charles River Laboratories, Wilmington, MA) 9 wk old with a body mass range of 115−135 g at the beginning of both experiments were used. Upon arrival from the supplier, hamsters were individually housed for 2 wk in polycarbonate cages (20 × 40 × 20 cm) with wire mesh tops and Alpha Dri bedding (Shepherd Specialty Papers, Kalamazoo, MI). The hamsters were housed in a vivarium with a room temperature of 20 ± 2°C and were exposed to a long-day photoperiod (14:10-h light-dark cycle, lights off at 1100). Hamsters were given food (PMI Rodent Diet no. 5001; Purina Mills, St. Louis, MO) and tap water ad libitum. After body mass and food intake were monitored for 1 wk, intruder and control hamsters were divided into groups matched for mean body mass and change in food intake. Only smaller hamsters 9 wk old (115−135 g) were used as intruders or nondefeated controls in both of these experiments, whereas older (>6 mo), larger (150−200 g) hamsters were trained and used as resident aggressors. Resident aggressors also were individually housed in polycarbonate cages (20 × 40 × 20 cm) with wire mesh tops and were given food (PMI Rodent Diet no. 5001) and tap water ad libitum upon arrival from the supplier. Only intruder and nondefeated control hamsters were handled daily throughout the study for ~3−4 min while body mass and food intake data were collected to aid in habituation to handling by the experimenter. All procedures were approved by the Georgia State University Institutional Animal Care and Use Committee and are in accordance with Public Health Service and United States Department of Agriculture guidelines.

**Agnostic Encounters**

On the day of defeat, animals were transported from the colony room to the behavioral testing room for the resident-intruder interaction. All testing occurred during the first 2 h of the dark phase of the light-dark cycle. Repeated social defeat consisted of placing the experimental (intruder) animals into the home of the aggressor (resident; Ref. 32) for 7 min. The interactions were closely monitored by a trained observer, and the behavior of the intruder was carefully noted. Hamster aggression is highly ritualized, with dominance or submission generally established within the first minute and maintained thereafter through social signals (e.g., flank marking) and social communication between the opponents (e.g., Ref. 20). The intensity of most agonistic encounters was moderate with some chasing and biting; however, an encounter was immediately stopped if an animal was bitten, drawing blood. In experiment 1, hamsters (n = 20: 10 nondefeated and 10 defeated) were defeated intermittently 15 times over a 34-day period for 7 min per daily session, whereas the controls just remained in their home cage. Hamsters were intermittently defeated such that there were six consecutive days of defeat followed by nine intermittent days of defeat to minimize adaptation to the social stress and minimize the predictability of the encounters. In experiment 2, in which we explicitly addressed the issue of the number of defeats needed to trigger the increases in food intake and body mass seen in experiment 1, the intruder hamsters were defeated one, four, or eight times over a 28-day period for 7 min per daily session, whereas the control animals remained in their home cage (n = 40: 10 nondefeated, 10 defeated once, 10 defeated 4 times, and 10 defeated 8 times). Because unpredictable bouts of stress in both humans and rodents have greater adverse effects than predictable stress (e.g., Refs. 23, 27), in experiment 3 we tested whether intermittent social defeat can alter body mass to a greater extent than consecutive defeats. Hamsters (n = 28: 10 nondefeated, 9 consecutively defeated, and 9 intermittently defeated) were defeated four times consecutively or four times intermittently over a 28-day period for 7 min per daily session, whereas controls remained in their home cage. For all pairings, experimental animals were rapidly attacked by the resident aggressor and displayed submissive behaviors toward the resident aggressor such as fleeing, tail lifting, and upright/side defense postures (12, 20) during the defeat session. No bites occurred that drew blood.

**Body Mass and Food Intake**

Beginning 1 wk before the first defeat, daily food intake (corrected for spillage and pouching) and body mass were measured to the nearest 0.01 g, and this continued throughout the remainder of all experiments.

**Experiment 1: Does Repeated Social Defeat Increase Food Intake, Body Mass, and WAT Mass in Male Syrian Hamsters?**

Blood collection and radioimmunoassay. On day 33, the hamsters were decapitated 5 min after the end of the final defeat. Trunk blood was collected in heparinized tubes, stored at 4°C overnight, and centrifuged the following day at 1,500 g for 20 min at 8°C, and the plasma was stored at −80°C until assayed. Cortisol (cortisol kit;
Diagnostic Systems Laboratories, Webster, TX) and testosterone (testosterone kit; Diagnostic Systems Laboratories) were measured. All kits were assayed according to the manufacturer’s instructions by the Endocrine Core Laboratory of the Yerkes Regional Primate Research Center (Emory University, Atlanta, GA). Sensitivity of the cortisol assay was 0.3 µg/dl, and that of the testosterone assay was 0.08 ng/ml. Intra-assay variability was <10% for both assays, and all samples for each hormone were run in a single assay.

Tissue harvesting. Inguinal, epididymal, retroperitoneal, and mesenteric WAT (IWAT, EWAT, RWAT and MWAT, respectively), as well as adrenal glands and testes were harvested and weighed to the nearest 0.001 g. The adrenals were snap-frozen in liquid nitrogen and stored at −80°C for subsequent assay of norepinephrine (NE) and epinephrine (Epi) content.

HPLC measurements of adrenal gland NE and Epi content. NE and Epi were measured using reverse-phase HPLC with electrochemical detection essentially according to our previously published method (43). Briefly, adrenal glands were thawed and homogenized in a solution containing 2 µg of dihydroxybenzoic acid (internal standard) in 0.2 M perchloric acid and 1.25 g/ml ascorbic acid (PCA/AA). After centrifugation, catecholamines were extracted from the homogenate with the homogenate with alumina and eluted into PCA/AA. The extracts were diluted 1:200, and catecholamines were assayed using an HPLC system with electrochemical detection (Cuocholem II; ESA, Bedford, MA). The mobile phase was Cat-A-Phase II, and the column was a C-18 reverse-phase column. Results are expressed as nanograms of NE or Epi per gram of adrenal tissue.

**Experiment 2: Are Repeated Resident-Intruder Interactions Necessary to Increase Body Mass and Food Intake?**

Because all animals were inadvertently not given food on the final day of the experiment, no meaningful terminal measurements could be obtained. Thus only food intake and body mass data are presented for experiment 2.

**Experiment 3: Do Intermittent Defeats Increase Adiposity and Food Intake More Than Consecutive Defeats?**

Blood collection and radioimmunoassay. On day 28 the hamsters were decapitated, and trunk blood was collected in heparinized tubes, stored at 4°C overnight, and centrifuged the following day at 1,500 g for 20 min at 8°C, and the plasma was stored at −80°C until assayed. Insulin (insulin kit; American Laboratory Products, Windham, NH) and leptin (leptin kit; Diagnostic Systems Laboratories) were measured. All kits were assayed according to the manufacturer’s instructions by the Endocrine Core Laboratory of the Yerkes Regional Primate Research Center. Sensitivity of the insulin assay was 0.07 ng/ml, and that of the leptin assay was 0.05 ng/ml. Intra-assay variability was <10% for both assays, and all samples for each hormone were run in a single assay.

Tissue harvesting. IWAT, EWAT, RWAT, and MWAT, as well as testes, thymus, and spleen were harvested, weighed to the nearest 0.001 g, and returned to the carcass to be processed for composition analysis.

Carcass composition analysis. The carcasses were processed for carcass composition analysis according to the method of Leshner et al. (21). Briefly, carcasses were dried to a constant weight at 85°C to determine carcass water. The dehydrated carcasses were ground finely in a blender, and lipid content was determined gravimetrically by using petroleum ether to extract the lipid from a homogeneous sample from each carcass. The remaining dehydrated and delipidated tissue was termed fat-free dry mass (FFDM).

Statistical Analysis

Body mass and food intake measurements in experiments 1–3 were analyzed using repeated-measures ANOVA. Feed efficiency for all experiments was analyzed using one-way between-subjects ANOVA (SPSS for Windows, release 11.5.0; SPSS, Chicago, IL). In experiment 1, WAT, testes, and adrenal masses, as well as adrenal NE and Epi contents and plasma cortisol and testosterone concentrations were analyzed using one-way between-subjects ANOVA. In experiment 3, WAT, thymus, spleen, and paired testes masses, plasma insulin and leptin concentrations, and absolute and relative carcass components were analyzed using one-way between-subjects ANOVA. For all experiments, differences among groups were considered statistically significant if *P < 0.05*. Exact probabilities and test values were omitted for simplicity and clarity of presentation of the results.

**RESULTS**

**Experiment 1: Does Repeated Social Defeat Increase Food Intake, Body Mass, and WAT Mass in Male Syrian Hamsters?**

Agonistic behavior. Because residents were larger than intruders, they reliably attacked and defeated the intruders. All of the defeated animals displayed frequent submissive and defensive behaviors during the resident-intruder pairings, and dominant-subordinate relationships remained stable across encounters.

Body mass, food intake, and feed efficiency. In experiment 1, defeat significantly increased intruder body mass compared with the nondefeated controls beginning with day 24 and continuing through the end of the experiment (*P < 0.05*; Fig. 1A). Cumulative food intake was significantly increased for the defeated hamsters compared with nondefeated controls beginning *day 8*, 1 day after the first social stress test and continuing until the end of the experiment (*P < 0.05*; Fig. 1B). Defeat significantly increased feed efficiency [body mass gained (g)/cumulative food intake (g); *P < 0.05*; Fig. 1C], a measure that reflects the relation between energy intake and energy stored, thereby inferring energy expenditure, in this case decreased energy expenditure by the defeated compared with the nondefeated hamsters.

WAT, testes, and adrenal masses and adrenal catecholamine content. IWAT, MWAT, and RWAT masses, but not EWAT mass, were significantly increased in defeated hamsters compared with controls (*P < 0.05*; Fig. 2). Paired testes mass (nondefeated: 3.36 ± 0.18 g; defeated: 3.48 ± 0.10 g) and adrenal mass (nondefeated: 22.1 ± 0.8; defeated: 22.7 ± 0.8 mg) were not affected by defeat.

Adrenal gland NE content (*P < 0.05*; Table 1), but not Epi content, was significantly increased in defeated compared with control hamsters. Plasma cortisol and testosterone concentrations were not affected by defeat (Table 1).

**Experiment 2: Are Repeated Resident-Intruder Interactions Necessary to Increase Body Mass and Food Intake?**

Body mass and food intake. A single defeat did not affect body mass (Fig. 3A); however, four consecutive days of defeat resulted in significantly increased body mass beginning 7 days after the last defeat, compared with controls, and continuing until the end of the experiment (*P < 0.05*; Fig. 3B). Hamsters receiving eight defeats as two groups of four consecutive days of defeat separated by six days also had significantly increased body mass compared with nondefeated controls beginning *day 21* (7 days after the end of the first set of 4 defeats [i.e., on the first day of the second set of 4 defeats]) and continuing until the
end of the experiment ($P < 0.05$); except days 22 and 25, which approached significance ($P < 0.06$ for each; Fig. 3C). The magnitude of the body mass increase induced by the four vs. eight defeats was not different, suggesting that the additional four defeats did not augment the body mass increase triggered by the first four defeats (Fig. 3, B and C).

A single defeat did not affect cumulative food intake (Fig. 4A); however, four consecutive days of defeat significantly increased cumulative food intake compared with controls beginning on day 18 and continuing through the end of the experiment ($P < 0.05$; Fig. 4B). Hamsters defeated eight times had significantly increased food intake beginning on day 17 (3 days after the end of the first set of 4 defeats) and continuing throughout the experiment ($P < 0.05$; Fig. 4C). Defeat significantly increased feed efficiency ($P < 0.05$; Fig. 4D) of animals defeated four or eight times, but not once.

Experiment 3: Do Intermittent Defeats Increase Adiposity and Food Intake More Than Consecutive Defeats?

Body mass, food intake, and feed efficiency. Four agonistic encounters, whether consecutive (defeated on days 7–10) or intermittent (defeated on days 7, 10, 13, and 17), significantly increased the body mass of defeated hamsters compared with nondefeated controls by the last 2 days of the study (days 27 and 28; $P < 0.05$; Fig. 5A), but intermittent defeat did not exaggerate this increase. In addition, cumulative food intake, regardless of whether the defeats were consecutive or intermittent, was significantly increased in both defeated groups compared with nondefeated controls, although four consecutive defeats was significantly different from nondefeated controls by day 14 ($P < 0.05$; Fig. 5B), whereas four intermittent defeats was significant by day 16 ($P < 0.05$; Fig. 5B). Intermittent defeats did not cause a greater increase in cumulative food intake compared with consecutive defeats (Fig. 5B). Feed efficiency was significantly increased in both groups of defeated hamsters compared with nondefeated controls ($P < 0.05$; Fig. 5C), but the groups were not different from each other.

Absolute and relative carcass components. There was no difference in absolute carcass water or FFDM among controls or intermittently or consecutively defeated hamsters (Fig. 6A), but both defeated groups had significantly increased total carcass lipid compared with nondefeated controls ($P < 0.05$; Fig. 6A). The percent carcass lipid content was significantly increased and the percent carcass water content significantly decreased in both the consecutively and intermittently defeated hamsters compared with nondefeated controls ($P < 0.05$; Fig. 6B).
Neither of the defeat schedules altered the percent carcass FFDM (Fig. 6B).

WAT, thymus, spleen, and testes masses. Intermittent defeats significantly increased all WAT pad masses (P < 0.05; Fig. 7), whereas consecutive defeats significantly increased only MWAT and IWAT masses (P < 0.05; Fig. 7), with EWAT mass approaching significance (P < 0.60; Fig. 7) compared with that of consecutively defeated hamsters. Testes, thymus, and spleen masses were not affected by either schedule of defeats (Table 2).

Terminal insulin and leptin concentrations. Neither intermittent nor consecutive defeats altered terminal plasma insulin concentrations (Fig. 8), but both significantly increased terminal plasma leptin concentrations, and to the same extent, compared with nondefeated controls (P < 0.05; Fig. 8).

DISCUSSION

The results of the present experiments suggest that repeated social defeat of male Syrian hamsters triggers a sustained increase in food intake and body and fat mass compared with nondefeated home cage controls. Moreover, these effects also can be established with four daily consecutive defeats with additional defeats not contributing further to the increased food intake and body and lipid masses. In addition, the increased body mass triggered by social defeat was reflected as increased adiposity, as evidenced by increases in total carcass lipid and WAT mass, including IWAT, RWAT, MWAT, and EWAT. Finally, four intermittent (unpredictable) versus four consecutive (predictable) social defeats both produced similar social stress-induced increases in body mass, cumulative food intakes, feed efficiencies, carcass lipid, and plasma leptin concentrations. Although both intermittent and consecutive defeats significantly increased MWAT and IWAT masses, intermittent social defeats also significantly increased EWAT and RWAT masses, perhaps suggesting an enhanced adiposity response with unpredictable social stress.

The findings of the present study are reminiscent of the increases in food intake and body mass and lipid mass seen in group-housed Syrian (4, 10, 25) or Siberian hamsters (1). It is possible that these two social conditions share some common underlying behavioral mechanisms in that social defeat may have occurred in the group housing conditions and that perhaps this triggered the increases in body and lipid mass (1, 4, 10, 25) and food intake (1, 10) seen in those animals. Clearly, however, there are marked differences in the duration of social contact for the animals in the present study compared with those in the group housing studies (4, 10, 25). Specifically, the duration of the group housing was 7–14 (4, 25) or 22 wk (10) of constant interaction, whereas in the present study the contact was limited to 7 min per interaction, and in experiments 2 and 3, a modest four defeats were sufficient to produce the in-

### Table 1. Adrenal gland norepinephrine and epinephrine content and plasma cortisol and testosterone concentration in experiment 1

<table>
<thead>
<tr>
<th></th>
<th>Adrenal Norepinephrine Concentration, µg/gland</th>
<th>Adrenal Epinephrine Concentration, µg/gland</th>
<th>Plasma Cortisol Concentration, µg/dl</th>
<th>Plasma Testosterone Concentration, µg/ml</th>
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<tr>
<td>Controls (nondefeated)</td>
<td>160 ± 17</td>
<td>225 ± 13</td>
<td>2.87 ± 0.62</td>
<td>3.20 ± 0.45</td>
</tr>
<tr>
<td>Defeated</td>
<td>200 ± 17*</td>
<td>230 ± 10</td>
<td>2.12 ± 0.50</td>
<td>3.25 ± 0.49</td>
</tr>
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*P < 0.05 vs. nondefeated controls.
increased food intake and body mass. Thus, in the present study, a cumulative interaction of 28 min produced increased body mass and food intake in contrast to the potential for interactions of 70,560 – 141,120 (4, 25) or 221,760 min (10) in the group housing experiments. Clearly, any effects of social facilitation of feeding that occurred during the 7-min defeat tests in the present study would be minimal because the animals were interacting, not eating. Cumulative food intake was significantly increased in all three experiments, however, suggesting that a consequence of defeat was responsible for the hyperphagia.

The increased food intake in the present experiments is likely a major factor underlying the increased body and lipid mass in all three experiments; we had no direct measure of energy expenditure. Feed efficiency, however, was significantly increased in defeated hamsters compared with their nondefeated counterparts, strongly suggesting defeat-induced decreased energy expenditure. Energy savings due to huddling certainly did not happen in the present experiments, and the data from Borer et al. (4) suggest that even with constant contact for 7–14 wk, it was unlikely that reduced thermogenesis due to huddling/contact played an important role in their obesity.

As noted above, the increased body mass of the defeated hamsters was reflected in increased WAT masses when measured (experiments 1 and 3). These individually increased WAT pad masses collectively underlie the significantly increased total carcass lipid content seen in experiment 3 for both four consecutive and intermittent defeats, with lean body mass (total carcass water and FFDM) unchanged. Proportionally, this was reflected in relatively increased carcass lipid content and decreased carcass water, suggesting that social defeat stress can cause redistribution of body composition. Of the WAT pad masses that were increased by social defeat, MWAT, a visceral WAT pad, consistently had the greatest significant increase in mass between defeated and nondefeated controls. A similar, or at least seemingly related, effect is seen in adult humans, in which stress can cause site-specific inhibition of lipolysis, particularly in central abdominal adipose tissue (35), leading to increased visceral lipid accumulation. In addition, positive correlations occur among high cortisol levels, high perceived stress, and increased waist-to-hip circumference ratio (suggestive of visceral fat accumulation), indicating that increases in cortisol secretion caused by chronic stress can promote increased abdominal obesity (e.g., Ref. 33). Thus this feature of the adiposity associated with social defeat might be exploited to model stress-induced development of visceral obesity in humans.

Because social defeat causes increased body and fat mass, we measured two hypothesized adiposity signals: plasma insulin and leptin concentrations. Hyperinsulinemia is commonly associated with obesity, particularly visceral obesity, and can ultimately result in diabetes (for review, see Ref. 9). Because the defeated hamsters had significantly increased WAT compared with nondefeated controls, we expected defeated hamsters also to have significantly greater circulating insulin con-
centrations, but they did not. Recently, however, we have observed significant increases in plasma insulin concentrations in socially defeated hamsters (unpublished observation). The reason for this discrepancy is not clear, given that control (nonstressed) plasma insulin concentrations were nearly identical between the studies.

By contrast, plasma leptin concentrations were significantly increased by social defeat whether it occurred intermittently or consecutively (experiment 3). This is consistent with the increased adiposity of both stressed hamster groups compared with nonstressed controls, an effect systematically replicated recently (unpublished observation). The finding of elevated plasma leptin concentrations associated with increased adiposity in the present (and unpublished) study is consistent with the general, but far from perfect [e.g., cold exposed laboratory rats (14)], positive relation between adiposity and circulating leptin concentrations frequently seen in laboratory rodents and humans (e.g., Refs. 8, 30). To our knowledge, there are no data explicitly testing the relation between circulating leptin and insulin concentrations in stress-induced obesity in humans with which the results of the present study could easily be compared.

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Fig. 5. A: daily absolute body mass (g; means ± SE) of Syrian hamsters intermittently or consecutively defeated 4 times over 28 days at 7 min per session in experiment 3. Controls were not defeated and remained in their home cage. Arrows above data points indicate the days that hamsters were intermittently defeated, whereas arrows below data points indicate the days they were consecutively defeated. *P < 0.05 vs. nondefeated controls. B: daily cumulative food intake of Syrian hamsters consecutively or intermittently defeated in experiment 3. #P < 0.05, consecutively defeated vs. nondefeated controls. *P < 0.05, intermittently or consecutively defeated vs. nondefeated controls. C: feed efficiency of consecutively or intermittently defeated hamsters in experiment 3. *P < 0.05 vs. nondefeated controls.

Fig. 6. A: absolute carcass water, lipid, and fat-free dry mass (FFDM) (g; means ± SE) for consecutively or intermittently defeated hamsters in experiment 3. *P < 0.05 vs. nondefeated controls. B: relative (% total carcass wet weight) carcass components (g; means ± SE) for consecutively or intermittently defeated hamsters in experiment 3. *P < 0.05 vs. nondefeated controls.
Defeated hamsters had plasma testosterone concentrations and paired testes masses similar to those of nondefeated controls. These data are consistent with group-housed laboratory rats living in a visible burrow system where subordinates subjected to long-term social stress have plasma testosterone and testes mass similar to dominants and to non-group-housed controls (3). There are, however, contradictory data showing that submissive rats in the visible burrow system have significantly decreased plasma testosterone concentrations compared with controls and dominants, with similar testes masses (40). Serum testosterone of defeated (submissive) Syrian hamsters can be decreased compared with dominant hamsters, but this effect appears to require longer duration and perhaps more intense interactions (16). Specifically, Syrian hamsters defeated five times do not have decreased plasma testosterone compared with dominant hamsters, but after nine defeats they do (16); moreover, the social stress was delivered twice a day for 15 min. Thus the effect of social stress on testosterone concentrations in laboratory rats and Syrian hamsters is not a simple one and may be related to the duration and/or intensity of the social stress.

Circulating cortisol concentrations of Syrian hamsters paired once with a dominant opponent are markedly increased compared with unpaired controls; however, this effect begins to diminish with increasing numbers of pairings until they are eventually not different from one another after nine pairings (16). These data are consistent with the results of the present study, in which there were no differences in terminal plasma cortisol concentrations between the social defeated hamsters and their nondefeated controls after 15 pairings across 33 days. By contrast, the elevated circulating corticosterone concentrations of socially stressed laboratory rats in the visible burrow system does not appear to attenuate with continuous social stress (3, 40).

Adrenal mass reflects the glucocorticoid- and mineralocorticoid-synthesizing cortex and catecholamine-synthesizing medulla and is a relatively crude proxy for overall stress effects. The adrenal mass of laboratory rats housed in the visible burrow system (3) or in group-housed female Syrian hamsters (25) is increased, apparently reflecting the increased activity of the hypothalamo-pituitary-adrenal axis. We expected to see a similar response in the present study; however, adrenal mass was not affected by social stress, perhaps because of differences in the duration and/or intensity of the relatively acute stress in the present experiments versus the chronic stress of other models. Despite no differences in adrenal mass between defeated and control hamsters in the present experiment, defeated hamsters had significantly higher adrenal NE, but not Epi, content. This finding of differential NE and Epi content in the adrenal medulla is not unique to this situation and is dependent on the type, magnitude, and duration of the stressor (for review, see Ref. 42). Moreover, the ability of the adrenal medulla to modulate independently NE or Epi synthesis/secretion is due to separate chromaffin cell populations that each synthesize only one of the catecholamines and that are differentially innervated by sympathetic preganglionics (28). How increased adrenal medullary NE content relates to the profile of social stress responses observed is unknown.

In humans, unpredictable events are more aversive than predictable events, causing greater alterations in homeostasis and thus increased stress (e.g., Ref. 23). In addition, previous research suggests that unpredictable events cause greater activation in central regions responsible for fear and anxiety in laboratory rats (e.g., Ref. 19) and reduction in immune function (27) compared with events that are predictable. Therefore, we expected that intermittent defeat would result in an exaggeration of the increased food intake and body and lipid mass compared with consecutive defeats; however, this did not occur. It is possible that intermittent defeat did not enhance the effects seen with consecutive defeats because the stressor was

### Table 2. Thymus, spleen, and paired testes masses of consecutively or intermittently defeated hamsters in experiment 3

<table>
<thead>
<tr>
<th>Groups</th>
<th>Thymus Mass</th>
<th>Spleen Mass</th>
<th>Paired Testes Mass</th>
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<tr>
<td>Control</td>
<td>0.055±0.002</td>
<td>0.141±0.006</td>
<td>3.572±0.098</td>
</tr>
<tr>
<td>4 Intermittent defeats</td>
<td>0.059±0.001</td>
<td>0.159±0.012</td>
<td>3.420±0.200</td>
</tr>
<tr>
<td>4 Consecutive defeats</td>
<td>0.088±0.002</td>
<td>0.142±0.004</td>
<td>3.452±0.152</td>
</tr>
</tbody>
</table>

Values are means ± SE.
not as intense as the typical stressor used for unpredictable and predictable stress studies in laboratory rats (i.e., noise or foot shock) or the duration of the social defeat stress (length of each interaction and/or the number of interactions) was not long enough to exaggerate these responses.

Across studies, however, the growth rate of nondefeated controls and subsequent alterations in body mass of defeated hamsters varied in their magnitude to some extent and may result from the so-called “batch effects” of hamsters shipped from the supplier. That is, Syrian hamsters within the same batch from the supplier likely are quite complementary to one another in energy-related responses, but it is a well-known phenomenon that comparison among multiple batches proves difficult. For example, previous studies investigating exercise-induced hyperphagia in Syrian hamsters observed variations in activity levels, food intake, and somatic growth between experimental groups from different batches (e.g., Refs. 5, 34).

Collectively, the results of this present study show that social stress produced by subjecting Syrian hamsters to the resident-intruder model reliably triggered increased food intake and body and lipid mass. Therefore, social defeat, a natural stressor, mimics many of the effects of nontraumatic stress in humans by increasing food intake and adiposity, including enhancement of visceral fat growth, and may prove useful in determining the mechanisms underlying this form of obesity.

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