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Direct innervation of white fat and adrenal medullary catecholamines mediate photoperiodic changes in body fat

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Demas, Gregory E. and Timothy J. Bartness. Direct innervation of white fat and adrenal medullary catecholamines mediate photoperiodic changes in body fat. *Am J Physiol Regulatory Integrative Comp Physiol* 281: R1499–R1505, 2001.—Seasonal adjustments in Siberian hamster adiposity are triggered by day length changes [i.e., short "winter-like" days (SDs) elicit body fat decreases vs. long "summer-like" days (LDs)]. These and other white adipose tissue (WAT) mass decreases traditionally have been ascribed to lipolysis triggered by sympathetically mediated, adrenal medullary released epinephrine; however, recent evidence suggests that direct sympathetic innervation of WAT also is important. Therefore, the contributions of WAT sympathetic innervation and adrenal medullary catecholamines to SD-induced decreases in adiposity were tested. Siberian hamsters were surgically bilaterally adrenal demedullated (ADMEDx) or sham ADMEDx, and all had one inguinal WAT (IWAT) pad sympathectomized via locally injected guanethidine, with the contralateral pad serving as a within-animal innervated control. One-half of the hamsters remained in LDs; the remainder was transferred to SDs. Guanethidine and ADMEDx abolished IWAT norepinephrine and adrenal epinephrine contents, respectively. Although sympathetic denervation or ADMEDx alone did not block SD-induced decreases in IWAT mass, their combination did. These results suggest that both adrenal catecholamines and the sympathetic innervation of WAT interact to decrease SD-induced decreased adiposity.

norepinephrine; adipose tissue; body weight; denervation; sympathetic nervous system; white adipose tissue; Siberian hamsters; sympathectomy; guanethidine; obesity

THE REGULATION OF ENERGY BALANCE involves a complex suite of hormonal and neural mechanisms controlling both energy input and output. When energy demands outweigh energy input, body fat stores [in the form of triglycerides stored in white adipose tissue (WAT)] are mobilized to compensate for the resulting energetic deficit (33). In contrast, excessive energy input results in increased adiposity, a condition not readily reversed in most animals, especially humans. Some animal species, however, pass naturally and effortlessly between the obese and lean states on an annual basis (31, 32). In some of these species, seasonal cycles of obesity and leanness are under environmental control, primarily by changes in the ambient photoperiod (day length; see Refs. 6 and 8). These changes in total body fat can be studied conveniently by mimicking naturally occurring day length changes within the laboratory. Our research has focused on one photoperiodic species, Siberian hamsters (*Phodopus sungorus*), a species that is naturally obese when housed in long "summer-like" days (LDs) and undergoes marked (~30–40%) reductions in body fat when exposed to short "winter-like" days (SDs; see Refs. 3, 7, 9, and 42).

Despite the large fluctuations in body fat displayed by seasonally breeding rodent species, very little is known about the precise physiological mechanisms underlying these impressive photoperiod-induced changes in adiposity (for reviews, see Refs. 6 and 8). In more traditional models of obesity, the majority of studies have focused on the role of humoral factors, primarily adrenal catecholamines, in the regulation of lipolysis (e.g., see Refs. 21 and 23). One major reason for this emphasis is that the addition of epinephrine (Epi), the primary catecholamine secreted by the adrenal medulla, to isolated white adipocytes in vitro stimulates lipolysis in the absence of nervous system influences (43). Because of this robust stimulation of lipolysis by Epi, neural contributions to WAT lipolysis seem to have been overlooked traditionally. There also are circulating factors, such as insulin (e.g., Refs. 13 and 22), that oppose the lipolytic effects of catecholamines, resulting in overall changes in the level of lipid mobilization from WAT pads. Despite these important humoral-mediated factors that affect lipolysis, more recent neuroanatomic and physiological evidence has accumulated in support of the direct innervation of WAT by the sympathetic nervous system (SNS; for review, see Refs. 4 and 5).

In terms of neuroanatomic evidence for the direct innervation of WAT by the SNS, we and others (e.g., see Ref. 35) have provided compelling evidence of significant sympathetic innervation (for review, see Refs. 4 and 5). For example, injections of the retrograde tract tracer Fluoro-Gold in inguinal WAT (IWAT) and epididymal WAT (EWAT) revealed labeling of apparent postganglionic SNS neurons in the sympathetic chain (45). This innervation was bidirectionally confirmed by

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injecting the anterograde tract tracer DiI in the sympathetic chain and subsequently visualizing rings of fluorescence around individual adipocytes (45). In addition, we characterized the central nervous system (CNS) sympathetic outflow from the brain to both IWAT and EWAT in laboratory rats and Siberian hamsters using a transneuronal viral retrograde tract tracer (pseudorabies virus) injected in WAT (2). Specifically, retrogradely labeled cells were identified throughout the neural axis, including classically defined spinal cord and brain stem sympathetic control structures [e.g., intermediolateral nucleus and central autonomic nucleus in the spinal cord; C1 and A5 adrenergic cell groups and rostral ventrolateral and ventromedial medulla in the brain stem] and forebrain areas previously implicated in body fat control (e.g., arcuate, suprachiasmatic, and paraventricular nuclei; see Ref. 2).

In terms of physiological evidence for the direct innervation of WAT by the SNS, cold exposure increases norepinephrine (NE) turnover, a measure of sympathetic drive, and increases lipolysis in WAT in rats; these responses are not blocked by adrenal demedullation (ADMEDx; see Ref. 19). The lipid mobilization induced by electrical stimulation of specific medial hypothalamic sites also is not blocked by ADMEDx (24, 39). These and other data (e.g., see Ref. 30) suggest that NE from sympathetic nerve endings terminating in WAT, and not circulating adrenal medullary catecholamines, mediate lipolysis in these lipid-mobilizing conditions. Furthermore, surgical denervation of the SNS nerves innervating WAT directly can attenuate fasting-induced lipid mobilization in rats (12), suggesting that these SNS nerves play an important role in lipid mobilization during food deprivation (14, 15). Finally, the ability of estradiol to mobilize lipid in ovariectomized laboratory rats is dependent on the SNS innervation of WAT (26, 45). Thus considerable physiological evidence supports an important role of the sympathetic innervation of WAT in lipolysis.

Sympathetic innervation of WAT appears to play a functional role in photoperiodic changes in body fat. For example, NE turnover is significantly increased in both EWAT and IWAT in Siberian hamsters housed in SDs vs. LDs (45); moreover, surgical denervation of IWAT in SD-housed hamsters partially, but not totally, blocks these SD-induced decreases in fat pad mass (46). Although the adrenal medulla does not seem necessary to trigger lipolysis under some conditions (see above), it should not be discounted entirely. Indeed, adrenal medullary catecholamines may account for the portion of the SD-induced lipolysis of Siberian hamsters not resulting from sympathetic innervation of WAT (46) and perhaps in other conditions stimulating lipolysis (e.g., see Ref. 39). Therefore, the purpose of the present experiment was to test the relative contributions of adrenal medullary catecholamines, and/or the direct sympathetic innervation of WAT, to SD-induced lipid mobilization in Siberian hamsters. This was accomplished by determining the effects of bilateral ADMEDx and unilateral chemical denervation of WAT, individually and in combination, on WAT pad mass in SD- and LD-housed hamsters.

MATERIALS AND METHODS

Animals and housing conditions. Adult (>60 days of age) Siberian hamsters (*Phodopus sungorus*) were obtained from our breeding colony at Georgia State University. This colony was originally derived from stock animals supplied by Dr. Bruce Goldman (University of Connecticut) in 1988 and interbred with wild-trapped hamsters in 1990 from Dr. Katherine Wynne-Edwards (Queens University). Finally, the colony was interbred with the hamsters supplied by Dr. G. Robert Lynch (University of Colorado) in 1995. These latter hamsters were derived from the original Hoffman colony but had been isolated for ~20 yr. Hamsters were weaned at 21 days of age and were housed with same-sex siblings. Before the start of the experiment (2 wk), animals were housed individually in polypropylene cages (27.8 × 7.5 × 13.0 cm) in colony rooms with a 16:8-h light-dark cycle (lights on 0300 Eastern Standard Time). Temperature was kept constant at 20°C, and relative humidity was maintained at 50 ± 5%. Food (Purina Rat Chow) and tap water were available ad libitum throughout the experiment. The bottoms of the cages were lined with corncob bedding and contained cotton nesting material.

Experimental design. Because WAT pads are unilaterally innervated, at least at the level of the postganglionic sympathetic neurons (45), they can be unilaterally denervated without affecting the integrity of the sympathetic innervation of their contralateral mate; thus, this nondenervated pad can serve as a within-animal control. Therefore, to test the role of the SNS innervation of WAT on SD-induced decreases in body fat, unilateral chemical denervations were achieved via microinjections of guanethidine (as described below) in the left IWAT pad (n = 40; referred to as experimental hamsters), whereas the contralateral pad was injected with saline vehicle. Note that, in preliminary studies, no differences were found between the left or right IWAT pads in either the ability of guanethidine to deplete NE or to block lipid mobilization (unpublished observations). One outcome of the expected unilateral denervation-induced increase in IWAT pad mass might also be a compensatory decrease in the mass of the contralateral innervated fat pad in an attempt to maintain overall body fat levels. To permit the detection of such a result, saline was injected bilaterally in IWAT of additional hamsters (n = 12 hamsters; referred to as control hamsters).

One-half of the experimental hamsters (n = 20) also received bilateral surgical ADMEDx (as described below), whereas the remaining experimental hamsters (n = 20) received sham ADMEDx. In addition, all of the control hamsters received bilateral surgical ADMEDx. After surgeries (2 wk), one-half of each group of experimental hamsters (n = 10/group) and one-half of the control hamsters (n = 6/group) were matched for age and body mass and transferred to SDs (8:16-h light-dark cycle). The remaining animals were kept in LDs (16:8-h light-dark cycle). Animals were kept in their respective photoperiods for 10 wk, and food intake and body mass were measured weekly. After 10 wk in their respective photoperiods, the animals were overdosed with pentobarbital sodium. To test whether the IWAT denervation elicited compensatory increases in the contralateral saline-injected fat pad or other nonmanipulated pads, as can happen with surgical removal of one of a pair of fat pads in this species (27), this pad was harvested along with the EWAT and retroperitoneal WAT (RWAT) pads in these experimental

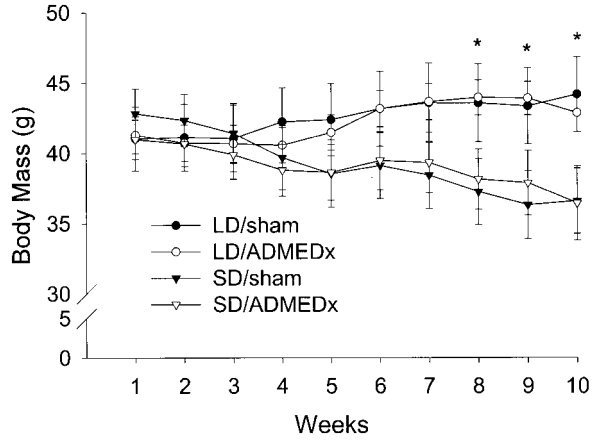

Fig. 1. Mean ± SE body mass (g) in hamsters that received bilateral adrenal demedullation (ADMEDx) or sham surgeries and were subsequently housed in long (LD) or short (SD) days for 10 wk. *Significant differences between means, $P < 0.05$.

hamsters and also in all of the control nondenervated hamsters. The paired testes were removed to test for responsiveness to the photoperiod (gonadal regression in SDs). In all animals, the entire adrenal gland (sham ADMEDx) or the remaining adrenal cortexes (ADMEDx) were removed for subsequent verification of the sham ADMEDx or ADMEDx surgeries. Hearts also were removed from all animals to serve as a nonadipose/adrenal control tissue. All tissues were rapidly weighed to the nearest 0.01 mg, immediately snap-frozen in liquid nitrogen, and then stored at −80°C for subsequent HPLC analysis (see below).

ADMEDx. ADMEDx was performed while the animals were anesthetized with pentobarbital sodium (50 mg/kg) according to a modification (10) of the method of Tonge and Oately (41). Briefly, bilateral incisions were made on the dorsum over the kidneys, and the adrenal glands were visualized using a dissecting microscope. A small incision was made on the adrenal cortex, and the adrenal medulla was extirpated using minimal pressure. Every effort was made to leave the adrenal cortex intact. The remaining adrenal tissue was removed and analyzed for Epi content by HPLC at the end of the experiment. Hamsters with adrenal Epi concentrations >0.05 ng/mg were excluded because they were considered to represent incomplete ADMEDx (see below for HPLC methodology).

Sympathetic denervation of IWAT. IWAT pads were chemically denervated with guanethidine sulfate based on the method of Demas and Bartness (17). Briefly, the fur was removed around the hindquarters of each animal, and the area was wiped with a 95% ethanol-soaked gauze pad. An incision was made dorsally on the skin from a point near the tail and lateral to the spinal column. The incision continued rostrally along the dorsum adjacent to the spinal column to a point immediately rostral to the hindimb and then laterally and ventrally to a point ~2 cm from the ventral midline. Finally, the incision extended caudally to a point near the tail. Care was taken with the depth of the incision to avoid cutting the underlying vasculature and musculature. The full extent of each IWAT pad was visualized, and a series of 20 microinjections (2 μl/injection) of guanethidine sulfate (10 μg/μl; Sigma Chemical, St. Louis, MO) dissolved in 0.9% saline were made using a microsyringe such that the full extent of the pad was covered. The needle was held at each injection site for ~30 s to minimize backflow. After the injections, IWAT pads were irrigated with saline, and the skin was closed with surgical staples. Nitrofurazone antibacterial powder was applied to the skin surface to prevent infection, and animals were returned to the colony room.

HPLC determination of catecholamine content. SNS denervation of IWAT and ADMEDx was verified by measuring NE content in IWAT and Epi content in adrenal tissue using reverse-phase HPLC with electrochemical detection according to the method of Youngstrom and Bartness (45) after Mefford (29). NE content was also determined in EWAT, RWAT, and heart for all animals. Briefly, tissue was thawed, weighed, and minced. A 250-mg sample was added to 1 ml of 0.3 M perchloric acid in microcentrifuge tubes, and 10 μl of dihydroxybenzoacetic acid was added to each sample and served as an internal standard. Tissue was further minced and then sonicated for 5 min on ice (5 times for each sample). Catecholamines were extracted from the remaining infranatant using alumina (200 mg/sample). The extracted samples were assayed using an ESA (Chelmsford, MA) HPLC system with electrochemical detection (guard cell: +35 mV; *cell 1*: +10 mV; *cell 2*: −30 mV). The mobile phase was Cat-A-Phase II purchased from a commercial supplier (ESA). Standard solutions were prepared at concentrations of 5.0, 3.3, and 1.65 ng/ml from commercially supplied standard kits (ESA) and were run at the beginning, in the middle, and at the end of each set of unknowns. Assay results were analyzed offline and expressed as nanograms NE per gram tissue.

Statistical analyses. Because the intact IWAT pads from unilaterally denervated ADMEDx hamsters did not differ in pad mass or NE content from control hamsters (hamsters that received bilateral ADMEDx but did not receive chemical denervation of either IWAT pad; see RESULTS), these intact, nondenervated pads served as within-animal controls for contralaterally denervated tissue in subsequent statistical analyses. Differences between experimental conditions were assessed via a 2 × 2 × 2 (photoperiod × surgery × IWAT pad treatment) mixed-model ANOVA (SigmaStat; Jandel Scientific, San Rafael, CA). Post hoc comparisons between means were conducted using Tukey's honestly significant difference tests when the overall ANOVA was significant. In all cases, differences between group means were considered statistically significant at $P < 0.05$. Exact probabilities and test values have been omitted for simplification and clarity of the presentation of the results.

RESULTS

Body and testes masses and food intake. SD-housed animals had significant reductions in both body and

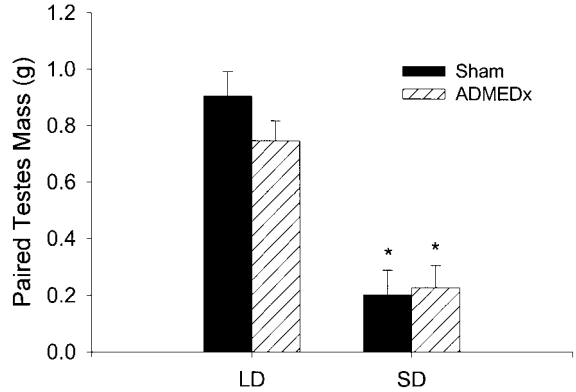

Fig. 2. Mean ± SE paired testes mass (g) in hamsters with ADMEDx or sham surgeries and subsequently housed in LD or SD days for 10 wk. *Significant differences between means, $P < 0.05$.

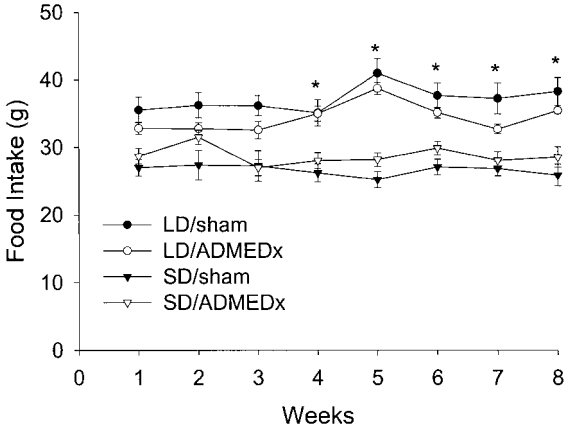

Fig. 3. Mean ± SE food intake (g) in hamsters with ADMEDx or sham surgeries and subsequently housed in LD or SD for 10 wk. *Significant differences between means, $P < 0.05$.

paired testes mass compared with LD-housed animals across weeks ($P < 0.05$; Figs. 1 and 2). SD-housed hamsters also demonstrated the typically reported (e.g., Refs. 9 and 42) natural reduction in food intake compared with their LD counterparts ($P < 0.05$; Fig. 3). Neither surgical denervation nor ADMEDx had any effect on body or paired testes mass or food intake among any of the experimental groups (Figs. 1–3).

IWAT pad mass and NE content. The intact IWAT pads from unilaterally denervated ADMEDx hamsters did not differ in pad mass or NE content from IWAT pads taken from nondenervated control hamsters. In addition, the nondenervated pads of unilaterally denervated ADMEDx hamsters did not differ from control animals in terms of either tissue masses or NE content of EWAT, IWAT, or heart (Tables 1 and 2).

Guanethidine treatment nearly abolished IWAT NE content compared with nondenervated IWAT from all groups ($P < 0.05$; Fig. 4). Neurally intact IWAT NE content was significantly elevated in SD-housed, adrenal medulla-intact hamsters compared with IWAT pads from corresponding LD-housed hamsters ($P < 0.05$ Fig. 4). NE content was significantly increased in neurally intact IWAT in ADMEDx LD- but not SD-housed hamsters compared with their adrenal medulla-intact, same-photoperiod counterparts ($P < 0.05$; Fig. 4).

SD-housed hamsters had significantly reduced IWAT pad mass compared with LD-housed animals ($P < 0.05$; Fig. 5). Guanethidine-induced sympathetic denervation, however, significantly increased (~2-fold) IWAT pad mass approximately twofold in both photoperiods compared with the nondenervated pad ($P < 0.05$). ADMEDx alone had no effect on IWAT pad mass in either photoperiod (Fig. 5). Combined ADMEDx and guanethidine-induced sympathetic denervation in SD-housed animals resulted in IWAT pad masses that were significantly larger than nondenervated IWAT pads from either ADMEDx or sham-operated animals housed in SDs ($P < 0.05$; Fig. 5) and, moreover, were not significantly different from the combination of treatments in LD-housed hamsters.

Both EWAT and RWAT pad masses were significantly reduced in SDs compared with LDs ($P < 0.05$; Table 1). In addition, SDs increased tissue NE content in EWAT and heart and IWAT in nondenervated pads ($P < 0.05$; Table 2). ADMEDx increased RWAT pad masses in both LDs and SDs ($P < 0.05$). Neither EWAT nor heart mass was affected by ADMEDx in either photoperiod (Table 1). ADMEDx increased NE content in EWAT in both LDs and SDs ($P < 0.05$). ADMEDx had no effect on NE content in the heart (Table 2).

DISCUSSION

The present data suggest that the sympathoadrenal system plays an important role in SD-induced lipid mobilization in Siberian hamsters. Neither guanethidine-induced sympathetic denervation of IWAT nor ADMEDx alone significantly blocked the SD-induced decrease in IWAT pad mass; however, both guanethidine-induced sympathetic denervation and ADMEDx interacted to completely block the SD-induced reductions in IWAT pad mass. Taken together, the results of the present study suggest that both the direct sympathetic innervation of WAT and adrenal medullary catecholamines (presumably Epi) interact to produce the SD-induced decrease in body fat in Siberian hamsters. In addition, the present results suggest that the process of fat storage and mobilization is not simply a

Table 1. *Tissue masses*

	Left EWAT Pad Mass	Right EWAT Pad Mass	Left RWAT Pad Mass	Right RWAT Pad Mass	Left IWAT Pad Mass	Right IWAT Pad Mass	Heart Mass
LD/sham	0.508 ± 0.056	0.503 ± 0.054	0.074 ± 0.008	0.073 ± 0.007	1.268 ± 0.157	0.712 ± 0.065	0.271 ± 0.014
LD/ADMEDx	0.432 ± 0.026	0.434 ± 0.027	0.127 ± 0.019*	0.122 ± 0.019*	0.948 ± 0.081*	0.517 ± 0.112*	0.253 ± 0.011
SD/sham	0.235 ± 0.051*	0.228 ± 0.052*	0.029 ± 0.003†	0.029 ± 0.037†	0.412 ± 0.095†	0.211 ± 0.046†	0.223 ± 0.008
SD/ADMEDx	0.253 ± 0.062*	0.258 ± 0.065*	0.041 ± 0.009†	0.040 ± 0.009†	0.799 ± 0.191*	0.242 ± 0.040†	0.225 ± 0.014
LD/control	0.320 ± 0.036	0.314 ± 0.037	0.082 ± 0.009	0.078 ± 0.008	0.773 ± 0.041*	0.507 ± 0.083*	0.212 ± 0.007
SD/control	0.149 ± 0.017	0.149 ± 0.016*	0.037 ± 0.005†	0.036 ± 0.056†	0.234 ± 0.176†	0.245 ± 0.027†	0.239 ± 0.012

Values are means ± SE; units are g. EWAT, epididymal white adipose tissue (WAT); RWAT, retroperitoneal WAT; IWAT, inguinal WAT; LD/sham, long-day, sham operated; LD/ADMEDx, long-day adrenal demedullated; SD/sham, short-day, sham operated; SD/ADMEDx, short-day adrenal demedullated. All animals received unilateral chemical denervation of the left IWAT pads except for the LD/control and SD/control animals, which received bilateral injections of saline. Statistical comparisons were made across experimental groups within each tissue type. Values with no symbols or sharing the same symbol are statistically equivalent. Values with different symbols are significantly different at $P < 0.05$.

Table 2. *Tissue NE content*

	Left EWAT NE Content	Right EWAT NE Content	Left IWAT NE Content	Right IWAT NE Content	Heart NE Content
LD/sham	32.62 ± 2.27	29.91 ± 2.69	2.747 ± 0.94	32.019 ± 4.70*	176.60 ± 11.91
LD/ADMEDx	41.27 ± 1.98*	39.32 ± 1.87*	2.667 ± 1.19	43.166 ± 4.67*	172.01 ± 9.79
SD/sham	41.45 ± 3.23*	39.73 ± 3.29*	3.158 ± 1.10*	48.769 ± 4.51*	240.86 ± 16.92*
SD/ADMEDx	49.47 ± 2.99†	50.63 ± 3.58†	3.268 ± 1.33*	45.767 ± 3.65*	237.47 ± 15.03*
LD/control	31.85 ± 2.28	34.49 ± 0.63	36.694 ± 2.51†	39.516 ± 2.07	146.46 ± 15.21
SD/control	34.28 ± 2.41	35.70 ± 1.85	41.002 ± 3.93†‡	39.658 ± 4.43	207.23 ± 7.89

Values are means ± SE; units are ng/g tissue. NE, norepinephrine. All animals received unilateral chemical denervation of the left IWAT pads except for the LD/control and SD/control animals, which received bilateral injections of saline. Values with no symbols or sharing the same symbol are statistically equivalent. Values with different symbols are significant at $P < 0.05$.

passive overflow mechanism controlled by food intake and energy expenditure. Rather, the CNS appears to play an active role in the regulation of total body fat via direct SNS outflow to adipose tissue. To our knowledge, this is the first test of the respective roles of the SNS innervation of WAT vs. adrenal medulla in the mobilization of lipid in any condition where lipolysis is known to increase. Previous studies have manipulated one of the two arms of the SNS and inferred the role of the remaining unmanipulated arm rather than testing it and/or testing the effects of the elimination of both arms (12, 15, 24, 26, 34, 40).

Substantial evidence demonstrates an important role of the sympathoadrenal system in the regulation of energy balance (25). For example, an inhibitory role of the SNS in the regulation of WAT pad mass has been suggested in several species after surgical denervation of WAT (for review, see Ref. 4). Specifically, unilateral denervation of the splanchnic nerves results in significantly larger pads on the side ipsilateral to the denervation compared with its neurally intact mate in several species, including cats, rabbits, and rats (12). The use of surgical denervation (axotomy) in these and other studies has important limitations because WAT also has sensory (18) but not parasympathetic (1) innervation; thus, surgical axotomy of WAT severs both sympathetic and sensory nerves, although the role of the latter is unclear (for review, see Refs. 4 and 5). Thus the specific function of the sympathetic innervation of WAT in the regulation of lipid mobilization cannot be unambiguously determined using surgically induced sympathectomy. In contrast, the guanethidine-induced sympathectomy of WAT reported here only renders the local sympathetic nerves innervating WAT nonfunctional, most likely sparing sensory innervation, based on studies in other tissues where guanethidine either did not change or increased the sensory-associated neuropeptides substance P and calcitonin gene-related peptide (11, 16).

The lack of a substantial effect by either adrenal demedullation or sympathetic denervation of WAT alone on SD-induced lipid mobilization, coupled with its complete blockade by the combined treatments, suggests that both adrenal medullary catecholamines and sympathetic innervation of WAT are involved in SD-induced body fat decreases in Siberian hamsters. One possible explanation for the lack of an effect by either manipulation alone on lipid mobilization is that the loss of one sympathetic system could result in compensation by the remaining, intact system (44). This notion appears to be supported in the present study by the significant increase in the NE content of

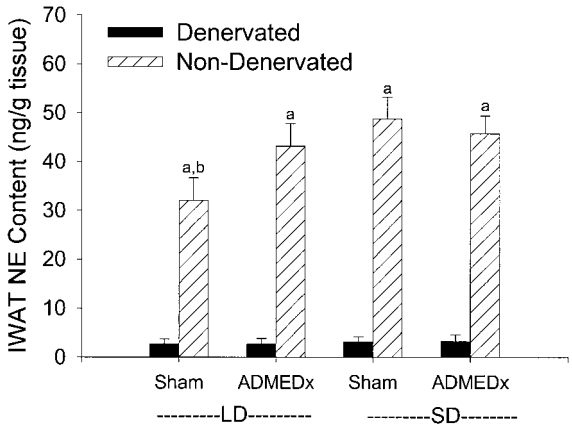

Fig. 4. Mean ± SE norepinephrine (NE) content (ng/g tissue) of both denervated and nondenervated pads in hamsters with ADMEDx or sham surgeries and subsequently housed in LD or SD days for 10 wk. IWAT, inguinal white adipose tissue. [a]$P < 0.05$ vs. nondenervated pads. [b]$P < 0.05$ vs. LD ADMEDx, SD Sham, and SD ADMEDx.

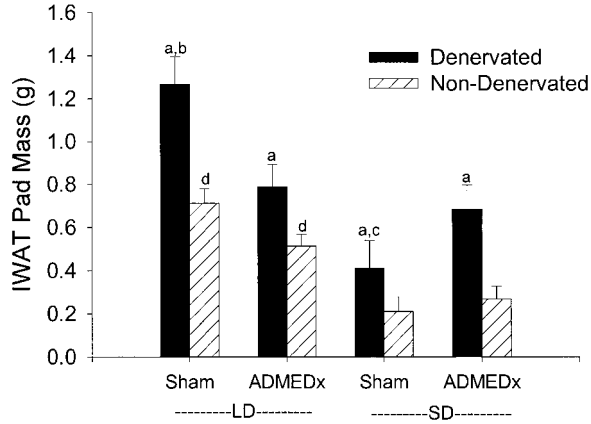

Fig. 5. Mean ± SE IWAT pad mass (g) of both denervated and nondenervated pads in hamsters with ADMEDx or sham surgeries and subsequently housed in LD or SD for 10 wk. [a]$P < 0.05$ vs. all nondenervated counterparts. [b]$P < 0.05$ vs. all comparisons. [c]$P < 0.05$ vs. denervated LD sham, denervated LD ADMEDx, and denervated SD ADMEDx groups. [d]$P < 0.05$ vs. nondenervated SD sham and SD ADMEDx groups.

neurally intact IWAT for LD-housed ADMEDx hamsters compared with their sham-operated counterparts. Although the underlying cause of the increase in NE cannot be determined in the present study, it seems likely to be the result of increased SNS activity, based on the typical increase in WAT NE content that normally is coupled with an increase in WAT NE turnover (e.g., see Ref. 45). Moreover, NE turnover is increased in the pancreas and interscapular brown fat after ADMEDx (38), and Epi turnover is increased in the adrenal gland after systemic chemical sympathectomy produced by 6-hydroxydopamine (38). Thus compensation by the remaining intact system may counteract the effects of either denervation or ADMEDx alone. Regardless of the precise mechanisms, the present results suggest that the sympathoadrenal system plays a critical role in regulating SD-induced changes in body fat in Siberian hamsters. Collectively, these results support the notion that these two arms of the SNS (i.e., direct innervation of WAT and adrenal medullary catecholamines) appear to work in a coordinated manner, via an unknown process, to regulate these seasonal increases in lipid mobilization.

Perspectives

There is substantial evidence that the sympathetic innervation of WAT not only exists (for review, see Ref. 4) but also appears functionally important for the mobilization of lipid stores (for review, see Ref. 5). The contribution of adrenal medullary released catecholamines vs. catecholamines secreted from nerve terminals in WAT pads in other conditions of lipid mobilization (e.g., cold exposure, fasting, and exercise) is unknown, but attempts at separating the roles of each sympathetic arm seem possible with the use of relatively specific lesion methods such as those used in the present study. The selective control of each arm of the SNS by the brain is not without some support because electrical stimulation of certain CNS sites can result in selective increases in circulating NE or Epi, suggesting the separate secretion of NE by nerve terminals and Epi by the adrenal medulla (20, 36). Therefore, although transneuronal tract tracing methods have revealed that the SNS outflow from the brain to WAT (2) and from brain to the adrenal medulla (37) are more similar than different, the possibility of separate control of each SNS arm under different conditions of lipid mobilization seems plausible. Importantly, the functional role of the SNS in mediating lipolysis suggests that the body fat is regulated, at least in part, by the CNS and is not simply the net result of passive overflow or underflow of energy intake vs. energy expenditure. Thus we have recently proposed a body fat regulatory system that includes the SNS innervation of WAT and adrenal medullary catecholamines as correctional mechanisms in a feedback loop controlling adiposity levels (28).

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