Nutritional Neurosciences

Intermittent Food Deprivation Improves Cardiovascular and Neuroendocrine Responses to Stress in Rats

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ABSTRACT Stressful events may trigger disease processes in many different organ systems, with the cardiovascular system being particularly vulnerable. Five-mo-old male rats had ad libitum (AL) access to food or were deprived of food every other day [intermittent food deprivation (IF)] for 6 mo, during which time their heart rate (HR), blood pressure (BP), physical activity and body temperature were measured by radiotelemetry under nonstress and stress (immobilization or cold-water swim) conditions. IF rats had significantly lower basal HR and BP, and significantly lower increases in HR and BP after exposures to the immobilization and swim stressors. Basal levels of adrenocorticotropic hormone (ACTH) and corticosterone were greater in the IF rats. However, in contrast to large stress-induced increases in ACTH, corticosterone and epinephrine levels in AL rats, increases in these hormones in response to repeated immobilization stress sessions were reduced or absent in IF rats. Nevertheless, the IF rats exhibited robust hypothalamic/pituitary and sympathetic neuroendocrine responses to a different stress (swim). The IF treatment improved glucose metabolism, as indicated by lower basal levels of circulating glucose and insulin, but with maintenance of glucose and insulin responses to stress. We concluded that improvements in cardiovascular risk factors and cardiovascular and neuroendocrine stress adaptation occur in response to IF.   J. Nutr. 133: 1921–1929, 2003.

KEY WORDS: • energy restriction • cardiovascular disease • glucose metabolism • hypertension • sympathetic nervous system

Dietary and behavioral factors appear to have major influences on the risk of cardiovascular disease (1,2). The rising tide of obesity and a metabolic syndrome characterized by insulin resistance and hypertension in many countries throughout the world are attributed to overeating and decreased amounts of exercise (3). Accordingly, two interventions that have been reported to reduce blood pressure (BP)[2] and improve glucose metabolism in obese humans and in laboratory animals are low energy diets and physical exercise (4–6). However, the mechanism(s) by which low energy diets reduce the risk of cardiovascular disease are not clear. Dietary restriction [reduced energy intake or intermittent food deprivation (IF), with maintenance of micronutrients] can increase life span and reduce the incidence of age-related diseases including cancer, diabetes and kidney disease (7). The cellular and molecular mechanisms underlying the beneficial effects of dietary restriction regimens are beginning to be revealed and appear to involve diminished free-radical production and a mild cellular stress response, which induces the expression of

genes that enhance the ability of cells to cope with more severe stress (8). Physiological changes associated with dietary restriction that might benefit the cardiovascular system include increased insulin sensitivity and reductions in BP and triglycerides (5,6,9,10).

An impaired ability to adapt to physiological and psychological stress may contribute to the pathogenesis of several different disorders including cardiovascular disease (2). Accordingly, there has been intense interest in identifying ways of reducing exposure to stress or enhancing adaptation to stress. Data suggest that improved stress adaptation can be accomplished by physical exercise (11) and behavioral training methods such as biofeedback and meditation (12). Diet-restricted rats and mice have increased resistance to high temperature (13) and to a number of different toxins (14,15). However, the effects of dietary restriction on cardiovascular responses to stress are unknown.

MATERIALS AND METHODS

Animals and surgical implantation of transmitters. All animal procedures were approved by National Institute on Aging Animal Care and Use Committee. Male Sprague-Dawley rats were maintained on a 12 h light/dark cycle, with lights on at 0600 h and off at 1800 h daily, and were provided continuous access to water throughout the study. Rats were individually housed after surgical implantation with a telemetric transmitter, and were given ad

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[2] Abbreviations used: ACTH, adrenocorticotropic hormone; AL, ad libitum; BP, blood pressure; GRP-78, glucose-regulated protein-78; HPA, hypothalamic-pituitary-adrenal; HR, heart rate; HSP-70, heat shock protein-70; IF, intermittent food deprivation; IGF-1, insulin-like growth factor 1; SNK, Student-Newman-Keul.

libitum (AL) access to food until the experimental diets were initiated. A telemetry system (Data Sciences International, St. Paul, MN) was used to monitor behavioral and physiological variables: a TA11PA-C40 (C40) transmitter for monitoring general activity, heart rate (HR), and diastolic, systolic and mean BP; and a TA10ETA-F20 (F20) transmitter for monitoring general activity, HR, and core body temperature. Surgical implantations of transmitters were performed in 3-mo-old rats under isofluorane anesthesia using a six-station anesthesia system (SurgiVet, Waukesha, WI), which combines in one system the delivery of isofluorane anesthesia mixed with therapeutic oxygen and an optional evacuation system. For a C40 implant, the catheter tip was inserted upstream into the descending aorta between the renal arteries and iliac bifurcation. The catheter was secured with tissue adhesive at the insertion point. The body of the implant was inserted into the peritoneal cavity and sutured to the abdominal musculature at the incision site. For an F20 implant, the body of the implant was inserted into the peritoneal cavity and secured to the abdominal musculature at the incision site. The two biopotential leads were routed subcutaneously to the desired placement sites located lateral to midline of the chest. The tips of leads were placed within muscle tissue and secured with a suture. Rats were allowed to recover for at least 1 mo before initiation of the experimental diets.

Diets and experimental design. A total of 16 rats were divided into two groups (eight rats per group): one group was given AL access to a standard NIH-07 rat diet (Harlan Teklad, Indianapolis, IN), and the second group was fed the same food every other day, an IF regimen that lengthens the life span of rats and mice by ~30% (16). The study design involved analyses before diet initiation and during the 6-mo period after diet initiation (**Fig. 1**A). Before initiating the experimental diets, physiological variables were recorded for 72 h, and rats were then randomly assigned to one of the two diet groups. Physiological variables were recorded in rats under basal (nonstress) conditions and during and after stress sessions at designated times during the 6-mo study (Fig. 1A). Basal physiological variables were recorded continuously during a 72-h period. To examine responses to a stressor, the basal condition was recorded overnight before the treatment. On the day of the stress test, the rat was subjected to a restraint or cold-water swim at the indicated times before and after the initiation of the diet as outlined (Fig. 1A). All stress treatments were performed between 0900 and 1500 h. Blood samples were obtained immediately after the stress session.

Stress protocols. The immobilization stress was performed using a modified plastic DecapiCone restrainer (Braintree Scientific, Braintree, MA). Physiological variables were recorded for 10–20 min before the stress session, during the 1-h stress period, and for 1–2 h poststress. The rat was immediately returned to its cage, and the poststress physiological variables were recorded. In the test of the responses to a single immobilization stress, all rats were deprived of food overnight, and the stress sessions were performed between 0900 and 1300 h. During the 5-d period when responses to the immobilization stress sessions were tested, the feeding schedules were maintained as usual. For the IF group the first stress day was a feeding day, and accordingly, the last stress day (d 5) was also a feeding day. Blood samples were obtained immediately after the 1-h immobilization stress session. The swim stress was administered by placing the rat in a 170-cm diameter tank containing cold water (21–22°C) for up to 15 min. A video system (Videomex; Columbus Instruments, Columbus, OH) was used to determine total swimming time, distance and speed. Immediately after removal of the rat from the tank, a blood sample was taken from the tail vein, the rat was returned to its cage and physiological variables were recorded for 2 h. In the cold-swim stress test, both the IF and AL rats were tested after they had eaten.

Analyses of blood samples. To eliminate possible effects of differences in food consumption status at the time of blood sampling, rats in both the IF and AL groups were deprived of food overnight before blood sampling. A volume of 2 mL of blood was drawn from the tail vein of each rat under anesthesia with isofluorane. The
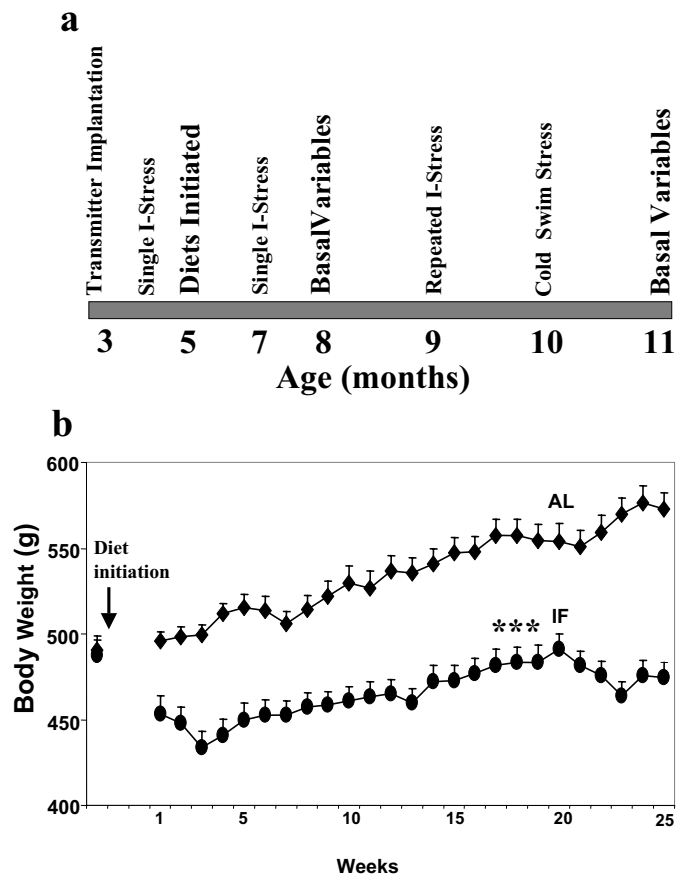

FIGURE 1 Experimental design and body weight changes in rats given ad libitum (AL) access to food or intermittent food deprivation (IF). (*A*) Timeline. Telemetry transmitters were implanted in 3-mo-old rats, diets were initiated 2 mo later, and physiological variables were under basal (nonstress) conditions at the indicated time points. Physiological variables were also recorded immediately before, during and after the indicated immobilization stress (I-stress) and cold-swim stress sessions. *B*, Body weights were measured weekly in AL and IF rats. Values are means ± SEM ($n = 8$). ***Different from AL, $P < 0.001$.

plasma was isolated and stored at −80°C. Plasma insulin (#008-10-1137-01; ALPCO Diagnostics, Windham, NH) and insulin-like growth factor 1 [(IGF-1) #DSL-10-2900; Diagnostic Systems Laboratories, Webster, TX] concentrations were measured by ELISA. Plasma glucose levels were measured using a Beckman glucose analyzer (Beckman Instruments, Fullerton, CA). The levels of adrenocorticotropic hormone (ACTH) and corticosterone in plasma were measured using radioimmunoassay kits (#07-106101 and #07-120102, respectively; ICN Diagnostics, Costa Mesa, CA). The concentrations of epinephrine and norepinephrine in plasma were measured using a catecholamine assay kit (#074-114602; ICN Diagnostics, Orangeburg, NY).

Statistical analyses. Data for physiological variables were analyzed using repeated-measures ANOVA followed by post hoc assessments with the Student-Newman-Keul's (SNK) test. One-way ANOVA followed by the SNK test or Student's *t* test was used for comparing hormone levels. A value of $P < 0.05$ was considered significant. Values in the text are means ± SEM.

RESULTS

Basal cardiovascular variables. Body weights of rats in the IF group were significantly less than those in rats that

were given AL access to food (Fig. 1b). IF rats consumed 30% less food over time than did AL rats (data not shown). There were no significant changes in activity, HR or body temperature in AL rats during the 6-mo period of the study (**Fig. 2**). However, BP was significantly greater at the 6-mo time point than at baseline in both IF and AL rats (P < 0.05).

IF rats had significantly lower basal HR and diastolic and systolic BP than did AL rats; this difference was evident within 1 mo of diet initiation (data not shown) and was maintained or enhanced during the 6-mo period (Fig. 2).

These changes in basal HR and BP are similar to those previously observed in rats on energy-restricted diets (17–19). The nighttime activity of IF rats was significantly less than that of AL rats, but daytime activity levels did not differ between groups (Fig. 2). Body temperature in IF rats was significantly lower than in AL rats. The reductions in HR, BP and nighttime activity of the IF rats were maintained across feeding and nonfeeding days (Fig. 2 and data not shown).

Cardiovascular and neuroendocrine responses to stress. The increases in both diastolic and systolic BP during 1 h of
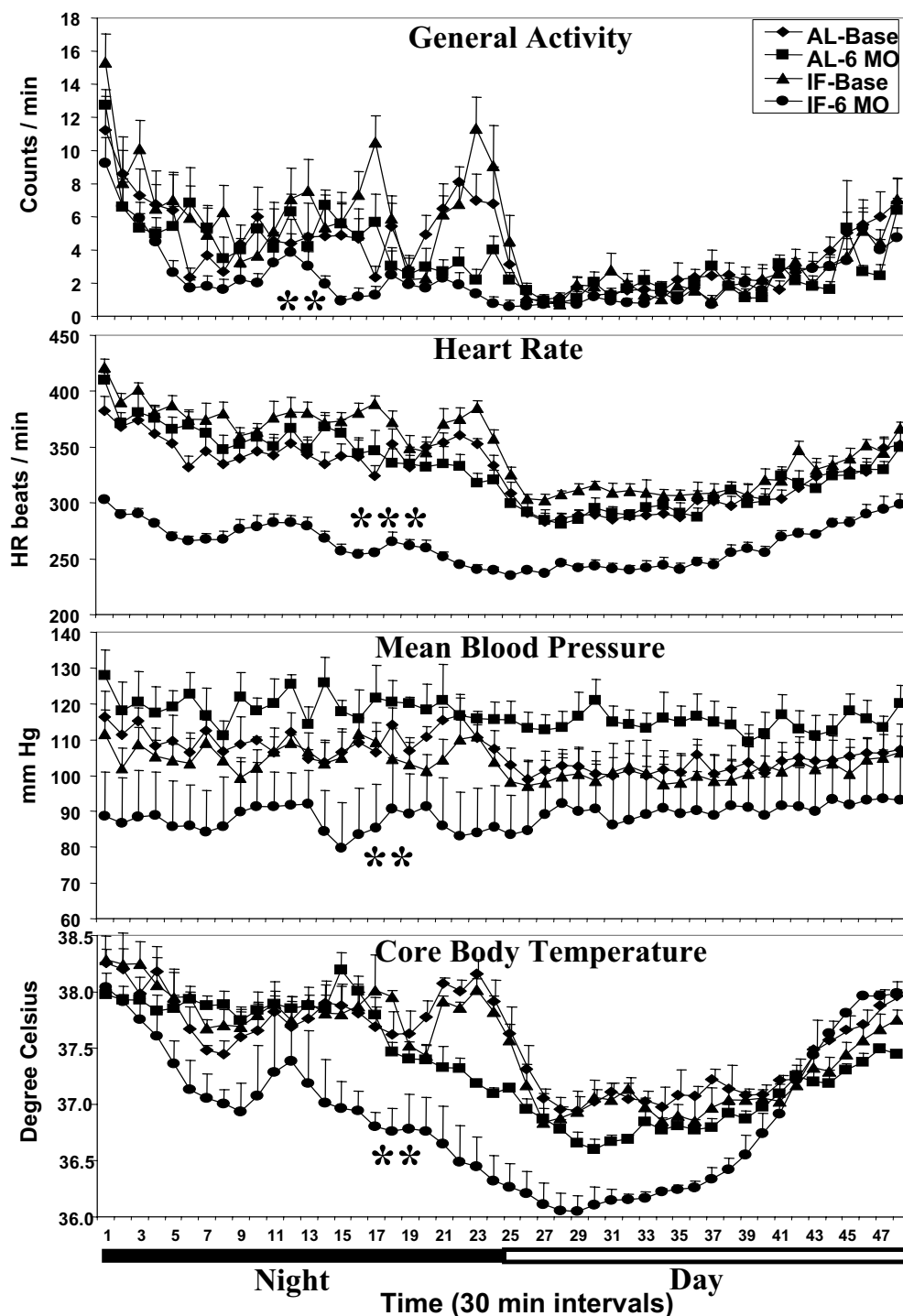

FIGURE 2 Intermittent food deprivation (IF) results in long-term reductions in blood pressure, heart rate (HR) and body temperature, without affecting levels of physical activity in rats. The recordings shown were taken before diet initiation (Base) and after 6 mo. Values are means ± SEM ($n = 8$). **Different from each of the other three diets/time points, $P < 0.01$. ***Different from each of the other three diets/time points, $P < 0.001$. AL, ad libitum.

immobilization stress were less in IF rats compared with their own responses before diet initiation and with the AL rats (**Table 1**). IF rats also exhibited a significantly reduced HR response to immobilization stress. Rats that had been on the IF regimen exhibited a reduced magnitude of responses of BP and HR after release from immobilization. Body temperature increased during immobilization stress, and the magnitude of the increase was lower in the IF rats compared with that of the AL rats (Table 1). After release from stress, the body temperature in IF rats was less than in AL rats. There were no significant differences between the groups in activity after release from the immobilization stress.

IF rats had consistently lower HR and BP during and after each stress period compared with those of AL rats (**Fig. 3** and data not shown). The amounts by which HR and BP were lowered during and after stress in IF rats became greater with increasing numbers of daily stress sessions (Fig. 3). The recovery of HR and BP toward baseline levels was significantly accelerated in IF rats compared with rats given AL access to food. An adaptation to repeated stress was also indicated by the more rapid decrease in general activity of the IF rats in the poststress period compared with that of the AL rats. Body temperature was increased rapidly in response to immobilization in both groups, with no significant differences between the two groups across days of stress sessions (Fig. 3).

During the 15 min when the rats were in the water, the AL and IF groups spent similar amounts of time swimming and swam similar distances at similar rates, with no significant differences between the two groups: mean swimming time, AL = 14.5 ± 0.3 and IF = 14.1 ± 0.4 min; mean swimming distance, AL = 11,228 ± 952 and IF = 9092 ± 684 cm; mean swimming speed, AL = 770 ± 55 and IF = 646 ± 43 cm/min; n = 8 (AL) or 6 (IF). Immediately after the swim stress, HR and BP were increased in both groups of rats, but were maintained at significantly lower levels in IF rats compared with those of the AL rats (**Fig. 4**). Poststress activity levels were not different in IF and AL rats.

The weights of the adrenal glands in rats that had been maintained for 6 mo on AL and IF diets were not significantly different (AL, 72 ± 5 mg; IF, 68 ± 3 mg). Three mo after diet initiation, basal (nonstress) levels of ACTH and corticosterone were significantly greater in IF rats compared with those of AL rats (**Table 2**). The levels of ACTH and corticosterone were greater after a single immobilization stress in AL rats compared with those of IF rats (Table 2). In contrast, a single immobilization stress did not further increase ACTH levels in IF rats, despite an increase in corticosterone levels (Table 2). ACTH and corticosterone levels were significantly greater after the immobilization stress in AL rats that had been subjected to repeated daily immobilization stress sessions during a 5-d period compared with those of IF rats treated similarly. In contrast, neither ACTH nor corticosterone levels were increased in response to immobilization stress in IF rats that had been subjected to repeated daily immobilization stress, and indeed poststress ACTH levels were lower than the basal level of ACTH before the repeated daily stress period (Table 2). After the swim, stress levels of ACTH were significantly increased in both AL and IF rats (Table 2). Corticosterone levels were significantly increased after the swim stress in the AL group but were not significantly changed in the IF group. The differences in basal- and stress-induced ACTH and corticosterone levels between rats fed control and IF diets suggest that IF activates the hypothalamic-pituitary-adrenal (HPA) stress response system, while suppressing responses of this neuroendocrine system to more severe stresses.

Levels of epinephrine after immobilization stress were significantly lower in IF rats compared with those of AL rats, whereas there was no difference in norepinephrine levels measured in the same samples (**Table 3**). There was no significant difference in the epinephrine levels of AL and IF rats after the swim stress, whereas norepinephrine levels were significantly greater in IF rats compared with those of AL rats (Table 3). These data suggest that IF does not compromise sympathetic responses to a novel stress, but does enhance adaptation of the sympathetic nervous system to repeated bouts of the same stressor.

TABLE 1

Intermittent food deprivation reduces cardiovascular responses to immobilization stress in rats[1]

Diet	Restraint	Group[2]	Activity	Heart rate	Diastolic	Systolic	Temperature
			cpm	*bpm*	*mm Hg*		*°C*
Before diet initiation	Prestress[3]	AL	2.0 ± 0.9	297.5 ± 9.5	87.8 ± 3.8	124.9 ± 5.3	37.2 ± 0.1
		IF	0.9 ± 0.4	314.1 ± 5.8	85.9 ± 3.9	118.8 ± 5.4	37.1 ± 0.2
	During stress	AL	0 ± 0	410.7 ± 12.7	108.3 ± 1.1	148.5 ± 3.1	37.9 ± 0.1
		IF	0 ± 0	419.1 ± 9.0	107.7 ± 6.0	144.9 ± 5.4	38.0 ± 0.1
	Poststress	AL	4.5 ± 0.5	364.9 ± 8.4	94.7 ± 2.5	135.5 ± 4.3	37.1 ± 0.2
		IF	5.7 ± 0.6	369.6 ± 6.3	91.2 ± 5.3	130.8 ± 5.2	37.1 ± 0.3
After diet initiation	Prestress	AL	2.2 ± 1.1	278.8 ± 7.4	87.9 ± 3.7	125.9 ± 5.0	37.0 ± 0.1
		IF	2.2 ± 0.6	286.9 ± 13.9	84.9 ± 9.4	116.9 ± 10.9	36.7 ± 0.1*
	During stress	AL	0 ± 0	398.5 ± 10.5	107.4 ± 3.4	152.9 ± 4.1	37.4 ± 0.1
		IF	0 ± 0	380.1 ± 10.7**	101.1 ± 7.7*	138.3 ± 7.9*†	37.1 ± 0.1
	Poststress	AL	4.4 ± 0.6	376.7 ± 7.8	95.9 ± 2.1	138.5 ± 3.4	37.1 ± 0.1
		IF	3.3 ± 0.4	329.1 ± 11.9**†	84.8 ± 7.3*†	121.2 ± 8.3*†	36.9 ± 0.2

[1] Values are means ± SEM. Abbreviations: AL, ad libitum; bpm, beats per min; cpm, counts per min; IF, intermittent food deprivation.
[2] The number of rats included in the each of the measurements of both groups: for activity and heart rate, n = 8; for diastolic pressure, systolic pressure and body temperature, n = 4.
[3] The time periods for pre-, during, and poststress were 20 min, 1 h, and 1.5 h, respectively.
* Different from IF before diet, $P < 0.05$. ** Different from IF before diet, $P < 0.01$. † Different from AL stress, $P < 0.05$.
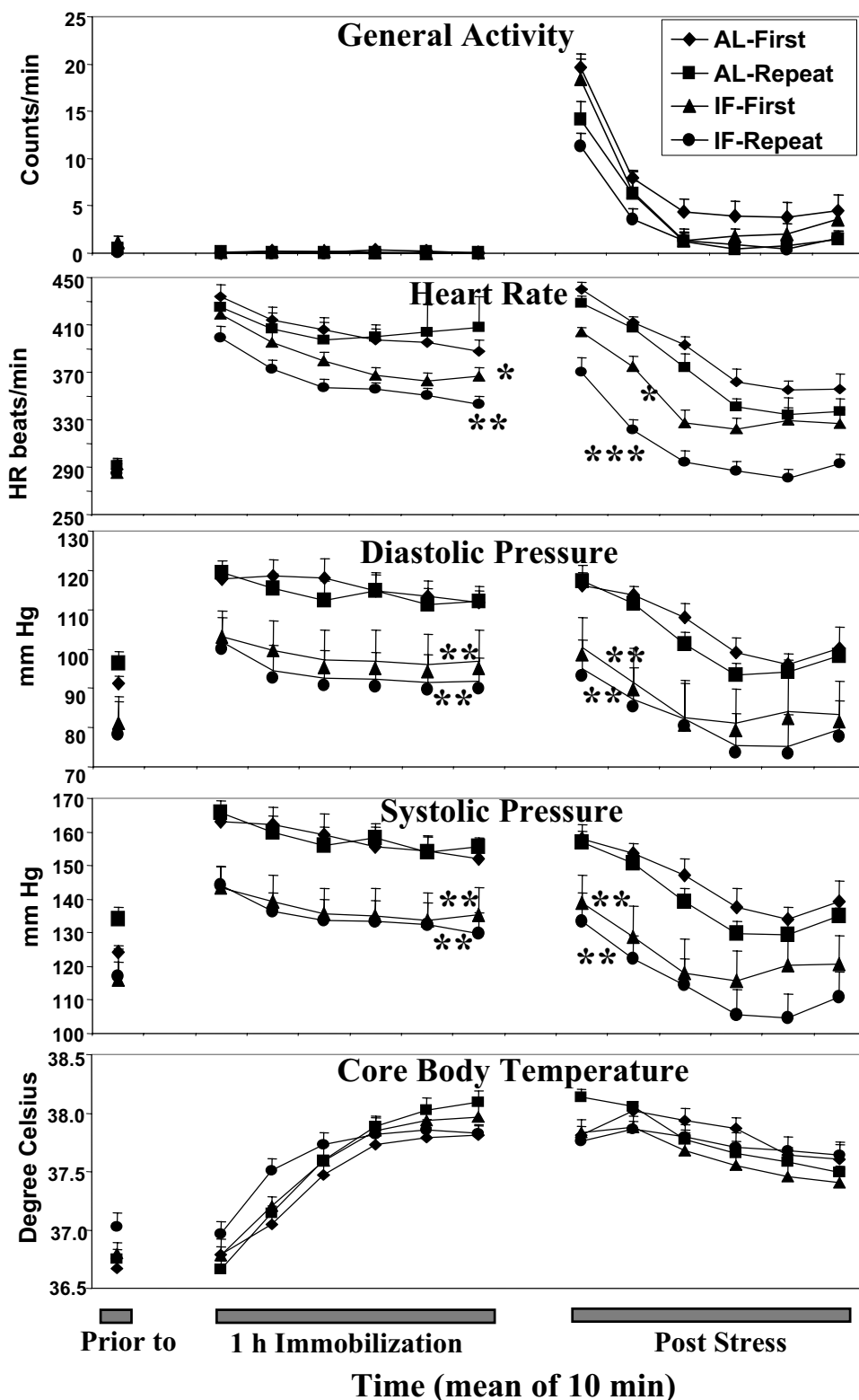
FIGURE 3 Cardiovascular responses to stress are attenuated in intermittently food deprived (IF) rats. Physiological variables were measured before, during and for 1 h after either the first immobilization stress or after the last of five daily immobilization stress sessions (multiple) in rats that had been given ad libitum (AL) access to food or had been IF for 4 mo. Shown is a comparison of the variables recorded on d 1 of immobilization stress (first I-S) with those recorded on d 5 of immobilization stress (fifth I-S). Values are means $\pm$ SEM ($n = 8$). *Different from AL, $P < 0.05$. **Different from AL, $P < 0.01$. ***Different from AL, $P < 0.001$. HR, heart rate.

Glucose metabolism. Plasma concentrations of glucose and insulin were significantly lower in IF rats compared with those of AL rats at 3 mo after diet initiation (**Table 4**). The IF and AL groups did not differ in their plasma concentrations of IGF-1. The concentrations of glucose and insulin were significantly increased to similar levels after a single immobilization stress in both IF and AL rats (Table 4). Plasma glucose and insulin concentrations were also increased to similar levels after the last day in a series of daily immobilization stress sessions, and after a cold-water swim stress in rats in both the IF and AL groups (Table 4). Collectively, these data demonstrate that IF reduces plasma glucose and insulin levels under nonstress conditions suggesting improved insulin sensitivity, while metabolic responses to different types of stress are maintained in IF rats.
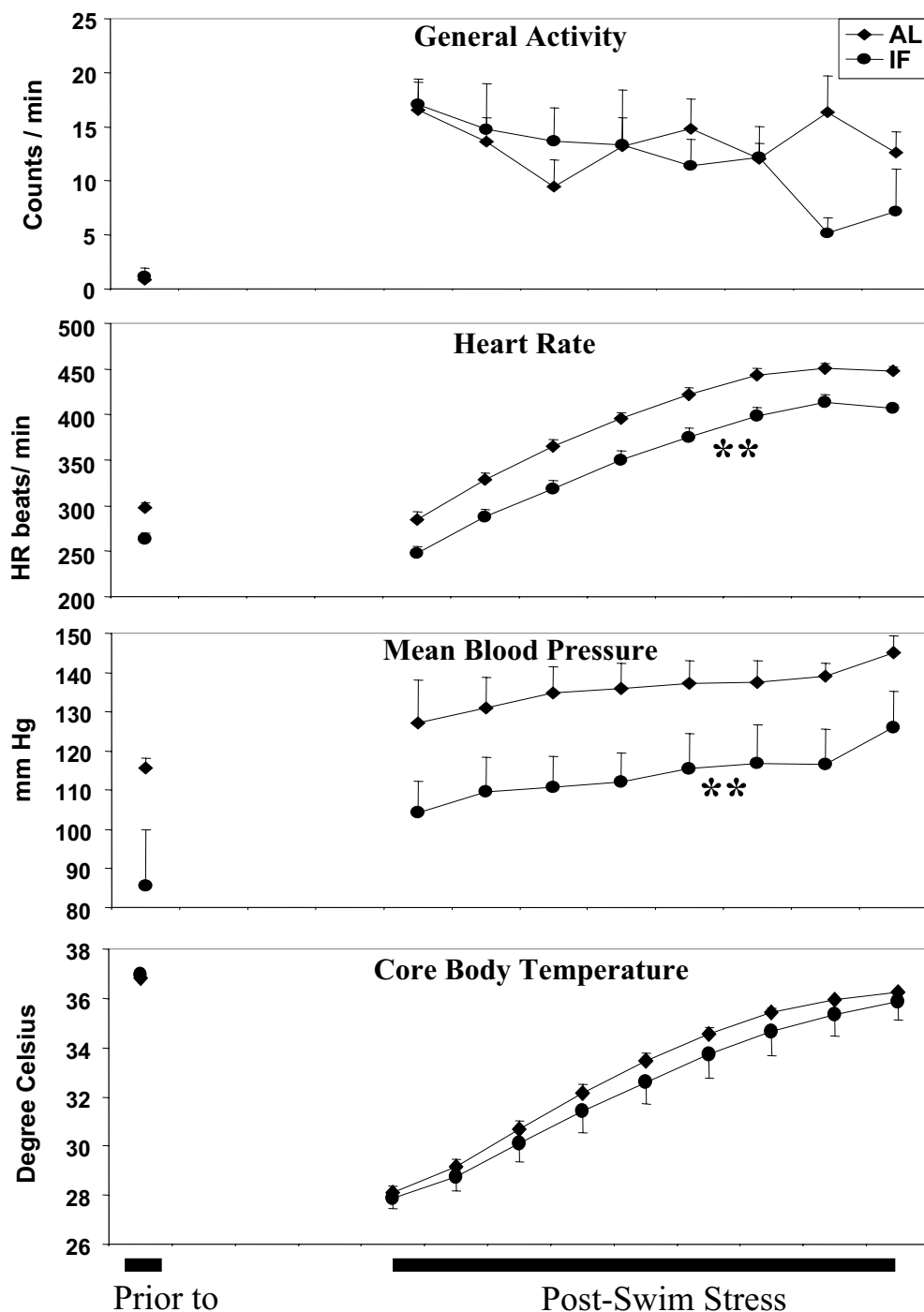
FIGURE 4 Intermittent food deprivation (IF) reduces cardiovascular responses to cold-water swim stress. Physiological variables were measured before and for 2 h after a cold-water swim in rats that had been given ad libitum (AL) access to food or were IF for 5 mo. Values are means ± SEM; n = 8 (AL) or 6 (IF). **Different from AL, P < 0.01. HR, heart rate.

DISCUSSION

The present findings demonstrate the beneficial effects of IF on cardiovascular and neuroendocrine responses to stress. IF rats exhibited reductions in resting BP and HR, and decreases in plasma levels of glucose and insulin. Because the risks of cardiovascular disease and stroke increase with increasing BP and glucose and insulin levels (20–23), our findings suggested the possibility that IF can reduce the risk of cardiovascular and cerebrovascular diseases. The magnitude of the effects of IF on BP, insulin and glucose levels documented in this study were equal to or greater than those previously obtained with exercise training regimens in rats (24) and humans (4). Because

there was no increase in the physical activity level of IF rats in this study, the effects of this dietary regimen on BP, HR and glucose and insulin levels were not mediated by increased amounts of exercise. To our knowledge, this study is the first to examine the effects of IF on cardiovascular physiological variables and glucose metabolism in rodents, and there have been no studies that have examined the effects of IF on BP and glucose metabolism in humans. Although it seems unlikely that most humans would be able to adhere to every-other-day food deprivation, they might be able to implement food-deprivation periods less frequently or reduce the number of meals eaten each day.

TABLE 2

Intermittent food deprivation modifies neuroendocrine responses to stress in rats[1]

	Group[2]	3 mo basal	Single restraint	Repeated restraint	Cold swim	6 mo basal
ACTH,[3]	AL	167.15 ± 26.95 (6)	308.47 ± 45.96† (6)	345.44 ± 90.47† (6)	360.35 ± 47.12† (7)	180.74 ± 21.35 (7)
pg/mL	IF	347.53 ± 69.91* (5)	293.71 ± 59.05 (6)	141.13 ± 20.29**†† (6)	661.56 ± 82.07**†† (5)	167.64 ± 35.03†† (6)
CORT,[4]	AL	242.51 ± 26.34 (6)	530.56 ± 20.38†† (7)	417.16 ± 36.17†† (6)	364.79 ± 21.82†† (6)	264.95 ± 32.26 (7)
ng/mL	IF	322.91 ± 22.69* (6)	580.59 ± 36.08†† (7)	264.19 ± 19.73** (7)	354.95 ± 25.78 (5)	118.29 ± 20.58**†† (5)

[1] Values are means ± SEM, (*n*). Abbreviations: ACTH, adrenocorticotropic hormone; AL, ad libitum; CORT, corticosterone; IF, intermittent food deprivation.
[2] 3 mo basal, 3 months basal level; 6 mo basal, 6 months basal level.
[3] Conversion factor: ACTH, pg/ml × 4.582 = pmol/L.
[4] Conversion factor: corticosterone, ng/mL × 2.886 = nmol/L.
* Different from corresponding AL value, $P < 0.05$. ** Different from corresponding AL value, $P < 0.01$.
† Different from the 3 mo basal value, $P < 0.05$. †† Different from the 3 mo basal value, $P < 0.01$.

Excessive exposure to uncontrollable stressors and/or the inability to adapt to stress are implicated in the pathogenesis of several different disorders including hypertension and atherosclerotic vascular disease (2,25). Moreover, acute stressors can trigger myocardial infarctions and strokes (26). Energy restriction has been reported to increase the resistance of organisms ranging from yeast and flies to rodents to several different stressors including heat and exposure to chemical toxins (14,15,27–29). Our findings showed that IF rats exhibited a marked improvement in cardiovascular stress adaptation as indicated by decreased BP and HR responses to immobilization stress. Interestingly, responses of the sympathetic nervous system to the stress were maintained or even enhanced in the IF rats. The ability of rats to mobilize glucose in response to stress, a critical mechanism for increasing energy availability to muscle cells, was also fully intact in IF rats. The reduction in the blood glucose level after repeated immobilization stress sessions in this study was most likely attributable to a general reduction of the stress response in the IF rats. However, it is certainly possible that the IF rats could have reduced levels of glycogen in their livers. Thus, it appears that IF greatly improves cardiovascular risk factors (reduced BP, and glucose and insulin levels) under nonstress conditions, reduces the hypertensive effects of acute and repeated stressors, while allowing normal activation of sympathetic and energy-mobilizing responses to stress. This conclusion is supported by a recent study showing that the decreased body weight, adrenal hypertrophy and thymic involution normally caused during an 8-wk period of daily immobilization stress (2 h/d) did not occur in rats that had been on a energy-restriction regimen before the stress period (30).

IF resulted in an intriguing complement of changes in stress-related hormones under basal and stress conditions. Basal (nonstress) levels of ACTH and corticosterone were increased in rats on the IF diet, indicating that IF results in a tonic activation of the HPA stress axis. In contrast, rats on the IF diet exhibited reduced ACTH and corticosterone responses to immobilization stress, particularly after repeated daily bouts of immobilization. These findings suggest that, as with other dietary restriction regimens (7), IF causes a tonic activation of the HPA axis. Other studies have shown that a similar IF regimen induces stress responses in cells that appear to account for the beneficial effects of IF in those tissues. For example, IF induces the expression of protein chaperones such as glucose-regulated protein-78 (GRP-78) and heat shock protein-70 (HSP-70) and neurotrophic factors such as brain-derived neurotrophic factor in brain cells, which play important roles in several beneficial effects of IF on the brain including increased resistance of neurons to oxidative and metabolic stress, and stimulation of neurogenesis (the production of new nerve cells from neural stem cells) (28,31). It is not known whether IF induces similar changes in cells of the cardiovascular system. However, it has been reported that aging results in a failure of ischemic-preconditioning effects on the heart, and food restriction preserves the ischemic-preconditioning response in rats (32), and a recent gene-profiling study is consistent with up-regulation of cytoprotective genes in animals on a energy-restricted diet (33).

The enhanced ACTH response to the swim stress in the IF rats compared with that of the AL rats shows that IF did not compromise the ability of the rats to respond to the stress. However, the fact that the levels of corticosterone in the same blood samples were not increased in the IF rats suggests that the adrenal cortex in IF rats may have a reduced sensitivity to ACTH. There was also an enhanced norepinephrine response to swim stress in the IF rats compared with that of the AL rats. Consistent with ACTH response data, the increased norepinephrine response showed that IF did compromise the ability of the rats to respond to the stress and suggests that IF enhances the responsiveness of the sympathetic nervous system.

Although this study was not intended to be a comparison of IF with low energy diets, such a comparison may prove interesting. Several previous studies, including our own, have shown that some biochemical and physiological effects in-

TABLE 3

Intermittent food deprivation modifies sympathetic responses to stress in rats[1]

	Group[2]	Repeated restraint	Cold swim
Epinephrine,	AL	323.54 ± 52.93 (5)	206.25 ± 44.71 (6)
pg/mL	IF	181.06 ± 29.13* (5)	196.65 ± 50.71 (5)
Norepinephrine,	AL	1.38 ± 0.18 (6)	2.93 ± 0.38 (5)
ng/mL	IF	1.30 ± 0.13 (5)	5.51 ± 1.18* (5)

[1] Values are means ± SEM, (*n*). Abbreviations: AL, ad libitum; IF, intermittent food deprivation.
[3] Conversion factor: epinephrine, pg/mL × 5.458 = pmol/L.
[4] Conversion factor: norepinephrine, ng/mL × 5.91 = nmol/L.
* Different from AL, $P < 0.05$.

TABLE 4

Glucose, insulin and IGF-1 levels in plasma in basal and in response to various stresses in rats[1]

	Group[2]	3 mo basal	Single restraint	Repeated restraint	Cold swim	6 mo basal
Glucose,	AL	143.50 ± 3.12 (8)	210.00 ± 7.22†† (8)	213.50 ± 10.21†† (8)	207.29 ± 14.58†† (7)	160.25 ± 11.86 (8)
mg/dL	IF	118.50 ± 1.93** (8)	199.43 ± 19.69†† (7)	193.13 ± 8.49†† (8)	215.60 ± 8.38†† (5)	120.83 ± 1.65** (6)
Insulin,	AL	122.98 ± 15.13 (5)	155.12 ± 16.30 (5)	148.31 ± 12.50 (6)	Not measure	133.27 ± 30.92 (5)
nmol/L	IF	70.66 ± 7.27* (5)	126.04 ± 10.11† (5)	139.66 ± 25.86† (7)	Not measure	74.79 ± 19.76* (5)
IGF-1,	AL	1991.64 ± 215.66 (7)	1698.65 ± 155.67 (6)	1787.33 ± 148.74 (7)	Not measure	2318.84 ± 220.71 (6)
ng/mL	IF	2035.43 ± 165.39 (7)	1697.45 ± 122.38 (6)	1527.02 ± 108.81 (6)	Not measure	1564.28 ± 176.41* (5)

[1] Values are means ± SEM, (*n*). Abbreviations: AL, ad libitum; IF, intermittent food deprivation; IGF-1, insulin-like growth factor-1.
[2] 3 mo basal, 3 months basal level; 6 mo basal, 6 months basal level.
[3] Conversion factor: Glucose, mg/dL ÷ 18 = mmol/L. Conversion factor: IGF-1, ng/mL × 0.13 = nmol/L.
* Different from AL, $P < 0.05$. ** Different from AL, $P < 0.01$.
† Different from the 3 mo basal value, $P < 0.05$. †† Different from the 3 mo basal value, $P < 0.01$.

duced by IF are similar to those induced by conventional energy restriction. For example, both IF and energy restriction decrease blood glucose and insulin levels, and increase corticosterone levels (7,34,35). However, differences have also been documented. For example, IF increases levels of ketone bodies (3-hydroxybutyrate), whereas energy restriction does not, and energy restriction decreases IGF-1 levels, whereas IF does not (34). With respect to the effects of IF and energy restriction on cardiovascular function, it was previously reported that energy restriction lowers resting BP and HR in rats (5), and our data document similar effects of IF on BP and HR in rats. Future direct comparisons of the two different dietary restriction regimens may provide novel insight into the mechanisms by which such diets benefit the cardiovascular and other organ systems.

Two cellular mechanisms that may play major roles in the anti-aging effects of dietary restriction are reduced free-radical production (7) and activation of signaling pathways that increase the resistance of cells to stress (8). Reduced levels of reactive oxygen species in many different tissues including liver, brain and heart have been documented in studies of rodents on energy-restricted diets (36,37). Increased oxidative stress in blood vessels and the heart occur in association with hypertension (38) and diabetes (39). Several observations suggest that an enhanced cellular stress resistance may also contribute to beneficial effects of IF on the cardiovascular system including studies showing that dietary restriction increases levels of cytoprotective stress proteins such as HSP-70 and GRP-78 in various tissues including the heart (33), and the fact that physical exercise stresses vascular and heart cells (40) and exerts similar effects to those of IF on BP and glucose metabolism (41,42 and the present study). Although future studies will be required to establish the underlying cellular and molecular mechanisms, the present data provide the first evidence that IF can improve cardiovascular stress adaptation, findings with important implications for preventing cardiovascular and cerebrovascular disease.

ACKNOWLEDGMENTS

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