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Metabolic consequences of chronic intermittent mild stress exposure

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Abstract

Chronic stress in humans has divergent effects on food intake, with some individuals reporting increased vs. decreased food intake during stress. This divergence may depend in part on stress intensity, with higher-intensity stressors preferentially promoting anorexia. Consistent with this idea, rodents given a high-intensity chronic variable stress paradigm have robustly decreased food intake and body weight gain. However, the metabolic effects of a less intense chronic stress paradigm are not clear. Thus in the present study, adult male rats were given chronic intermittent mild stress (CIMS) exposure (3 cycles, in which each cycle consists of once daily mild stress for 5 days/week for 2 weeks, followed by 2 weeks of no stress) vs. non-stress controls, combined with ongoing access to a palatable diet (PD; choice of chow, high-fat diet, 30% sucrose drink, and water) vs. control diet (chow and water). As expected, access to PD increased caloric intake, body weight gain, and adiposity, and impaired glucose tolerance. CIMS decreased body weight gain only during the first cycle of stress and did not affect body weight gain thereafter, regardless of diet. Moreover, CIMS did not alter total food intake, adiposity or glucose tolerance regardless of diet. Lastly, CIMS transiently increased high-fat diet preference in PD-fed rats during the first stress cycle. Collectively, these results suggest that CIMS has relatively modest metabolic effects that occur primarily during initial stress exposure. These results support the hypothesis that the metabolic consequences of chronic stress vary with stress intensity and/or frequency.

Keywords

chronic stress; diet preference; glucose tolerance; palatable diet; diet choice

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1. Introduction

There are complex interactions among stress, food intake and obesity, with stress often defined as real or perceived threats to homeostasis or well-being (reviewed in [1]). Stress exerts numerous effects on behavior, and also activates physiological stress responses. These physiological responses include activation of the hypothalamic-pituitary-adrenocortical (HPA) axis, resulting in increased circulating glucocorticoids, as well as increased sympathetic nervous system (SNS) tone (reviewed in [2]). Glucocorticoids work together with elevated SNS tone to exert numerous effects throughout the brain and body. Many of these effects (e.g., increased liver glucose output, increased release of fatty acids from white adipose tissue, and reduced insulin secretion) are focused on increasing the mobilization of energy to provide ready fuel for appropriate behavioral and physiological responses that maintain homeostasis and promote survival.

Given the profound effects that physiological stress responses have on behavior and metabolism, it is not surprising that stress is an important factor contributing to the regulation of food intake and energy balance. For instance, stress is linked with increased total food intake and the development of obesity in some groups of people, whereas stress decreases food intake and body weight in others [3–5]. The reasons for the discrepant effects of stress on food intake and energy balance are not clear, but one factor that might contribute is stressor intensity. For instance, high-intensity stressors that involve real threats to homeostasis (e.g., military combat, recently being the victim of violence) are often linked with anorexia, decreased appetite, and decreased body weight [6–8]. In contrast, hyperphagia often occurs with stressors that are likely less intense and involve more psychological threats to well-being – so called daily life stressors like school, work and interpersonal relationships [9–13]. Consistent with this idea, we and others have seen that rodents given a high-intensity chronic variable stress (CVS) paradigm (consisting of twice-daily stressors that include warm and cold water swims, restraint, hypoxia, and cold room exposure) have markedly decreased food intake and body weight gain throughout the duration of the chronic stress paradigm [14–16].

To test the hypothesis that the metabolic consequences of stress vary with the intensity of the chronic stress paradigm, the present work characterizes the metabolic (e.g., food intake, body weight, adiposity, glucose tolerance) effects of a low-intensity chronic stress paradigm. More specifically, a chronic intermittent mild stress (CIMS) paradigm is developed that modifies CVS in 3 important ways. First, it utilizes mild stressors that do not pose direct threats to homeostasis (e.g., cage tilt, dampened bedding, placement of a novel object into the home cage, etc.). Second, the stressors are given less often (e.g., 3 cycles in which each cycle consists of once daily stressors for 5 days/week for 2 weeks, followed by 2 weeks of recovery). Recovery periods were included to decrease the total number of stressors, and because intermittent stress-free periods have been implicated as important contributors to the metabolic effects of chronic stress [17]. Moreover, as some evidence suggests that the metabolic effects of stress interact with the consumption of highly-palatable foods [18, 19], the effects of CIMS are studied in rats concurrently eating a palatable diet (PD; free access to high-fat diet (HFD), 30% sucrose drink, chow and water) or control diet (free access to chow and water).

2. Materials and Methods

2.1 Subjects

Adult male Long-Evans rats (~250 g body weight) were purchased from Harlan Laboratories (Indianapolis, IN). Rats were singly-housed in a temperature- and humidity-controlled room with a 12-12 hour light cycle (lights on at 06:00 hours; lights off at 18:00 hours). Rats acclimated to the facility for at least 11 days (d) before experiment onset. All procedures were approved by the Institutional Animal Care and Use Committee at the University of Cincinnati and are compliant with the NIH Guide for the Care and Use of Laboratory Animals.

2.2 Diet treatments

At 4 days before experiment onset (denoted as day -4; Figure 1), all rats were weighed and body composition was determined by NMR (EchoMRI, Echo Medical Systems, Houston, TX). Rats were then divided into 4 treatment groups (n=12–13/group) that were matched for body weight and percent body fat (in order to ensure that all groups began the study with a similar metabolic status). Two of these treatment groups then began continuous access to PD, consisting of *ad libitum* access to HFD (15% calories from protein, 40% calories from fat, 46% calories from carbohydrate; D03082706, Research Diets, New Brunswick, NJ), normal chow (25% calories from protein, 17% calories from fat, 58% calories from carbohydrate; LM-485, Harlan-Teklad, Indianapolis, IN), 30% sucrose (MP Biomedicals, Solon, OH) drink, and water. The other 2 treatment groups were maintained on *ad libitum* normal chow and water as a control diet.

2.3 CIMS paradigm

At four days after initiation of the diet treatments (experiment day 0; Figure 1), one of each dietary treatment groups was randomly selected to receive CIMS, while the other group remained in their home cages as non-stress controls. CIMS consisted of 3 cycles of stress, in which each cycle comprised one daily mild stress exposure for 5 days/week for 2 weeks, followed by 2 weeks of recovery (no stress). Mild stressors were presented in an unpredictable order and included: overnight housing in home cage with water-dampened bedding; overnight housing in home cage tilted to ~30°; being transported (while in home cage) on a wheeled cart up and down the halls of the animal facility for 5 minutes (min); being placed in an open field for 5 min; placement of a novel object (e.g., plastic duplo block, nylabone, etc.) into the home cage for 30 min; and exposure to white noise at a moderate volume (similar to volume of human conversation) for 30 min.

2.4 Metabolic measures

Food intake (from all nutrient sources) and body weight were monitored throughout the study. In addition, adiposity (% body fat measured by NMR) and oral glucose tolerance were assessed at the end of each cycle of CIMS. For the oral glucose tolerance test, rats were fasted overnight and the following morning basal blood glucose (0 min) was measured by tail-clip using Precision Xtra glucometers and test strips (Abbott, Alameda, CA). After completing measurement of the basal time point, rats were immediately given an orogastric

gavage of 50% glucose solution (Fisher Scientific, Pittsburgh, PA) at a final dose of 1.5 g glucose per kg of body weight. At 15, 30, 60, and 120 min after glucose gavage, tail blood glucose was re-measured.

2.5 Statistical analyses

Data are shown as mean ± SEM. Statistical differences were determined by ANOVA (with repeated measures when appropriate) with protected Fisher's post-hoc analysis using GB-STAT software (Dynamic Microsystems, Inc., Silver Spring, MD). Statistical significance was taken as $p < 0.05$.

3. Results

3.1 Body weight and body weight gain

Body weight (Figure 2A) was monitored throughout the experiment and analyzed by 3-way ANOVA with repeated measures comparing Diet, Stress, and Day (repeated factor). This analysis showed main effects of Diet ($p=0.001$) and Time ($p < 0.001$) with a Diet X Time interaction ($p < 0.001$), but no main effect of Stress ($p=0.381$) and no other interactions (all $p > 0.05$). Post-hoc analysis identified increased body weight by PD beginning on experiment day 28. These data suggest that ongoing access to PD increased overall body weight and that this was not affected by exposure to CIMS.

In order to determine whether CIMS and PD affected body weight gain, this measure was determined for each cycle of CIMS and analyzed by 3-way ANOVA with repeated measures comparing Diet, Stress, and Day (repeated factor) (Figure 2B). This analysis showed main effects of Diet ($p < 0.001$) and Time ($p < 0.001$) with significant Stress X Time ($p=0.003$) and Diet X Time ($p < 0.001$) interactions, but without a main effect of Stress ($p=0.576$) or other interactions (all $p > 0.05$). Post-hoc analysis indicated that PD increased body weight gain. In addition, CIMS decreased body weight gain in both PD- and chow-fed rats, but only during the first CIMS cycle.

3.2 Total caloric intake

Total daily caloric intake from all nutrient sources (Figure 3A) was calculated and analyzed by 3-way ANOVA with repeated measures comparing Diet, Stress, and Day (repeated factor). Total daily caloric intake had main effects of Diet ($p < 0.001$) and Time ($p < 0.001$), with significant Diet X Time ($p < 0.001$) and Diet X Stress X Time ($p=0.025$) interactions, but with no main effect of Stress ($p=0.582$) and no Stress X Time interaction ($p=0.251$). Post-hoc analysis indicated that PD increased total daily caloric intake throughout the duration of the experiment regardless of CIMS exposure.

In order to determine the extent to which differences in total caloric intake were related to overall differences in body weight, we also analyzed caloric intake normalized to body weight (Figure 3B). ANOVA (3-way) comparing Diet, Stress, and Day (repeated factor) revealed a main effect of Diet ($p < 0.001$) and Time ($p < 0.001$) and a Diet X Time interaction ($p < 0.001$), with no main effect of Stress ($p=0.84$) and no other interactions (all $p > 0.05$). More specifically, post-hoc analysis showed that PD transiently increased

normalized caloric intake (until experiment day 28), with no effect thereafter regardless of CIMS exposure.

3.3 Food preference

Since PD-fed rats have free access to 3 different types of food (i.e., HFD, sucrose (30%) drink, and chow), they are able to choose how much of their total daily calories to consume from these food types. In order to determine whether CIMS affected this choice, we calculated chow, HFD and sucrose preference, where preference is the percentage of total daily calories consumed as each of these food types.

Chow preference (Figure 4A) was analyzed by 2-way repeated measures ANOVA comparing Stress and Day (repeated factor). This analysis indicated that chow preference increased over the experimental time course (main effect of time, $p < 0.001$) and was not affected by CIMS (no main effect of Stress, $p=0.691$, and no Stress X Time interaction, $p=0.732$). HFD preference (Figure 4B) was similarly analyzed; HFD preference decreased over the experimental time course (main effect of time, $p < 0.001$) and was not affected by CIMS (no main effect of Stress, $p=0.779$, and no Stress X Time interaction, $p=0.732$). Sucrose preference (Figure 4C) looked similar to chow preference; sucrose preference increased over the experimental time course (main effect of time, $p < 0.001$) and was not affected by CIMS (no main effect of Stress, $p=0.946$, and no Stress X Time interaction, $p=0.937$).

Since CIMS only transiently affected body weight gain (Figure 2B), we tested whether CIMS also transiently affected food preference in PD-fed rats. The extent of the CIMS-induced change in preference (i.e., the % preference of CIMS rats minus the average % preference of non-stress controls) was calculated for each food type (Figure 4D). These data were then analyzed by 2-way ANOVA with repeated measures comparing type of Food and Day (repeated factor). This analysis revealed a significant Food X Time interaction ($p=0.016$) without main effects of Food ($p=0.31$) or Time ($p=1.0$). More specifically, post-hoc analysis showed that HFD preference increased during the first 2 weeks of CIMS exposure.

3.4 Caloric efficiency

Since CIMS transiently reduced body weight gain during the first cycle of CIMS despite equivalent caloric intake, caloric efficiency (the amount of body weight gained per calorie consumed) was calculated and analyzed by 3-way ANOVA with repeated measures comparing Diet, Stress, and Day (repeated factor) (Figure 5). ANOVA identified a main effect of Diet ($p < 0.001$) and Day ($p < 0.001$), as well as Diet X Day ($p < 0.001$) and Stress X Day ($p=0.004$) interactions (with no main effect of Stress, $p=0.326$, and no Diet X Stress X Day interaction, $p=0.951$). Post-hoc analysis showed that PD-fed rats had increased caloric efficiency during cycles 1 and 2 of CIMS, regardless of stress exposure. In addition, CIMS reduced caloric efficiency during the first CIMS cycle regardless of diet type. Taken together, this suggests that PD may increase body weight gain in part by increasing caloric efficiency, while CIMS may reduce body weight gain in part by decreasing caloric efficiency.

3.5 Body composition

Percent body fat (i.e., adiposity) prior to experiment onset (Figure 6A) was analyzed by 2-way ANOVA and showed no main effect of Diet ($p=0.27$) or Stress ($p=0.145$), nor a Diet X Stress interaction ($p=0.631$), as expected since rats were assigned to treatment groups that were matched for pre-study body weight and percent body fat. After the first cycle of CIMS (Figure 6B), percent body fat was increased by PD (main effect of Diet, $p < 0.001$), but not affected by CIMS (no main effect of Stress, $p=0.919$, and no Diet X Stress interaction, $p=0.839$). Likewise, after the second cycle of CIMS (Figure 6C), percent body fat was increased by PD (main effect of Diet, $p < 0.001$), but not affected by CIMS (no main effect of Stress, $p=0.65$, and no Diet X Stress interaction, $p=0.81$). And again, after the third cycle of CIMS (Figure 6D), percent body fat was increased by PD (main effect of Diet, $p < 0.001$), but not affected by CIMS (no main effect of Stress, $p=0.657$, and no Diet X Stress interaction, $p=0.401$). Taken together, these results suggest that PD increased adiposity throughout the experiment regardless of CIMS exposure.

3.5 Glucose tolerance

Oral glucose tolerance tests were performed to assess the effects of PD and CIMS on glucose metabolism. These tests were performed at the end of each cycle of CIMS, with measurement of blood glucose levels and analysis by 3-way ANOVA with repeated measures, comparing Diet, Stress, and Time (repeated factor). At the end of first cycle of CIMS (Figure 7A), blood glucose showed a main effect of Diet ($p < 0.001$) and Time ($p < 0.001$), as well as a Diet X Time interaction ($p < 0.001$), but no main ($p=0.803$) or interactive (all $p > 0.05$) effects of Stress. Post-hoc analysis revealed that PD increased blood glucose at 15, 30, 60 and 120 min after oral glucose gavage regardless of CIMS exposure. Similar results were seen after the second (Figure 7B) and third (Figure 7C) cycles of CIMS, where blood glucose had a main effect of Diet ($p < 0.001$) and Time ($p < 0.001$), as well as a Diet X Time interaction ($p < 0.001$), but no main ($p=0.352$ for cycle 2, $p=0.787$ for cycle 3) or interactive (all $p > 0.05$) effects of Stress. Likewise, post-hoc analysis revealed that PD increased blood glucose at 15, 30, 60 and 120 min after oral glucose gavage regardless of CIMS exposure after both the second and third cycles of CIMS.

4. Discussion

4.1 Overall summary and conclusions

It has been suggested that the effects of chronic stress on food intake, energy balance and metabolism may be related to stressor intensity, with higher intensities preferentially promoting decreased food intake and negative energy balance. Consistent with this idea, high-intensity chronic variable stress (e.g., consisting of twice daily exposure to stressors that include warm and cold swims, hypoxia, cold room, restraint, and shaker) and chronic social stress (e.g., repeated, sustained episodes of social defeat) paradigms robustly decrease food intake and body weight gain in rats [15, 16, 20, 21]. In the present work we developed a low intensity chronic stress paradigm (that we term ‘chronic intermittent mild stress’ or CIMS) that decreases the frequency and intensity of each stressor exposure, while also allowing for repeated recovery periods. We then assessed the metabolic consequences of CIMS in rats that are maintained on normal chow vs. rats that had a palatable diet consisting

of free access to HFD, sucrose (30%) drink and chow. The results show that PD consumption resulted in a host of negative metabolic effects. These effects included increased caloric intake, increased caloric efficiency, body weight gain, and adiposity, as well as impaired glucose tolerance. In contrast, CIMS exposure had few metabolic consequences. More specifically, CIMS modestly decreased both body weight gain and caloric efficiency, and increased HFD preference, only during the first CIMS cycle. Taken together, these results suggest that the metabolic effects of chronic stress vary with the frequency and/or intensity of stressor exposure.

4.2 Effects of PD on food intake, energy balance and metabolism

The metabolic effects of the PD used in the present work are consistent with those that occur following other palatable diet paradigms. It is clear that diets high in fat and/or sucrose result in marked increases in caloric intake, body weight gain, caloric efficiency, adiposity, and glucose intolerance [22–25]. As expected, PD consisting of free access to HFD, 30% sucrose drink and chow mimicked these effects, confirming the effectiveness of the PD exposure. Of note, caloric intake normalized to body weight was only elevated during the first month of PD access, and recovered to chow-fed controls thereafter. This suggests a pattern of excessive food intake that occurs predominantly upon initial exposure to the palatable foods – a pattern that has been observed with other palatable food paradigms [23–25]. Also, when PD-fed rats were first offered the 3 nutrient sources (i.e., HFD, sucrose, and chow) they obtained the vast majority of their calories from HFD (~75%), with less from sucrose (~20%), and very little from chow (~5%). Over the duration of the experiment, these ratios changed so that by the end of study PD-fed rats obtained about ~50% of their daily calories from HFD, ~30% from sucrose, and ~20% from chow. Notably, this shift in food preference in response to sustained palatable food access was not affected by concurrent CIMS.

4.3. Effects of CIMS on food preference and body weight gain

When rodents are given a dietary choice that includes both a highly-palatable food (e.g., high in fat or sugar) and a low-palatability food (e.g., normal chow), they consume a large proportion of their daily calories from the highly-palatable food [19, 22, 25, 26]. When rodents given these same dietary choices are given concurrent CVS (or a similar high-intensity chronic stress paradigm), they often maintain their intake of the highly-palatable food while decreasing chow intake [19, 22]. This shift in the proportion of calories derived from highly-palatable foods is sometimes interpreted as a ‘comfort’ feeding response, and generally persists throughout the entire chronic stress paradigm [19, 22]. The present work showed that CIMS modestly increased preference for HFD (~7%) among PD-fed rats. Moreover, this effect was transient, occurring only during the first 2 weeks of CIMS exposure. This suggests that the ability of chronic stress to alter food preference towards high-palatability foods is related to the intensity of stress experienced, with higher intensity paradigms inducing more pronounced and sustained changes in HFD preference. Notably, CIMS did not increase preference for sucrose, despite its high palatability. This may be related to the specific macronutrient contents. For example, it could indicate that if both fat and sugar are available, stress preferentially promotes fat intake. Alternatively, this may be related to the degree of palatability, hedonics or reward provided. For example, if the HFD

was considered more palatable than both the sucrose and chow, then stress might shift intake towards the most-preferred food type available (e.g., HFD), and away from all others. Future work can be directed towards discriminating between these 2 possibilities.

High-intensity chronic stress paradigms induce a marked decrease in body weight that generally persists throughout the stress exposure [19, 22, 26]. Moreover, this effect is generally accompanied by reduced total caloric intake and reduced caloric efficiency, suggesting that diminished body weight gain results from both reduced caloric intake and increased energy expenditure [19, 22, 24]. In contrast, CIMS caused a modest decrease in body weight gain (~11–12%) that occurred only during the first CIMS cycle and occurred regardless of diet. Notably, this diminished body weight gain during CIMS occurred despite equivalent caloric intake, and was accompanied by reduced caloric efficiency, suggesting that it may have resulted from a transient increase in energy expenditure – a possibility that can be addressed in future work using indirect calorimetry. Taken as a whole, these data suggest that the magnitude and duration of chronic stress effects on body weight, as well as the role that increased energy expenditure plays in this phenomenon, are related to the intensity of chronic stress experienced.

Lastly, the present work focused on the metabolic outcomes of mild chronic stress (CIMS). Physiological and behavioral stress end points were not included due to concerns that the stress associated with these procedures would itself interfere with metabolic status. Future work can address the extent to which CIMS evokes various stress outcomes (e.g., elevated glucocorticoids, sympathetic tone, anxiety-related behaviors, etc.), as this work may provide insight into possible mediators underlying the actions of CIMS on HFD preference, caloric efficiency and body weight gain.

4.4 Perspectives

Chronic stress evokes varying effects on food intake, with about 35–60% of people reporting increased food intake during stress, while about 25–40% of people report decreased food intake [3–5]. The divergent effects of stress on food intake and energy balance are likely caused by multiple factors [1]. The present work suggests that stressor intensity and/or frequency may be one factor contributing to these differences.

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Highlights

- Chronic intermittent mild stress (CIMS) transiently decreased body weight gain.
- CIMS transiently increased high-fat diet preference.
- CIMS did not alter total caloric intake, adiposity or glucose tolerance.
- Metabolic effects of chronic stress are likely related to its intensity/frequency.

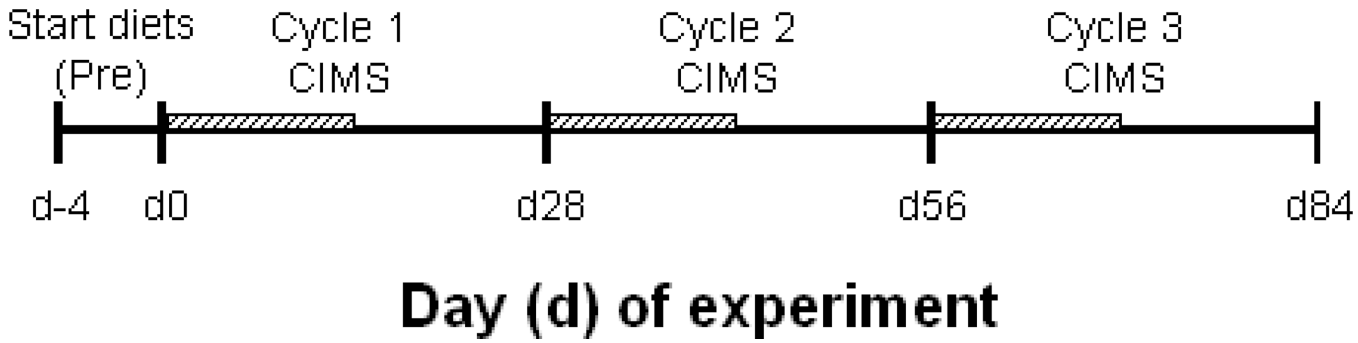

Figure 1.

Schematic of experimental timeline. At 4 days prior to experiment onset (day -4), rats began continuous access to either palatable diet (PD; *ad libitum* access to high-fat diet, 30% sucrose drink, normal chow and water) or control diet (*ad libitum* access to normal chow and water). The experiment (onset on day 0) consisted of 3 cycles of chronic intermittent mild stress (CIMS), in which each cycle comprised once daily mild stress for 5days/week for 2 weeks (*denoted as hatched bars*), followed by 2 weeks of recovery (no stress). Non-stressed control rats did not receive stress exposure and instead remained undisturbed in their home cages.

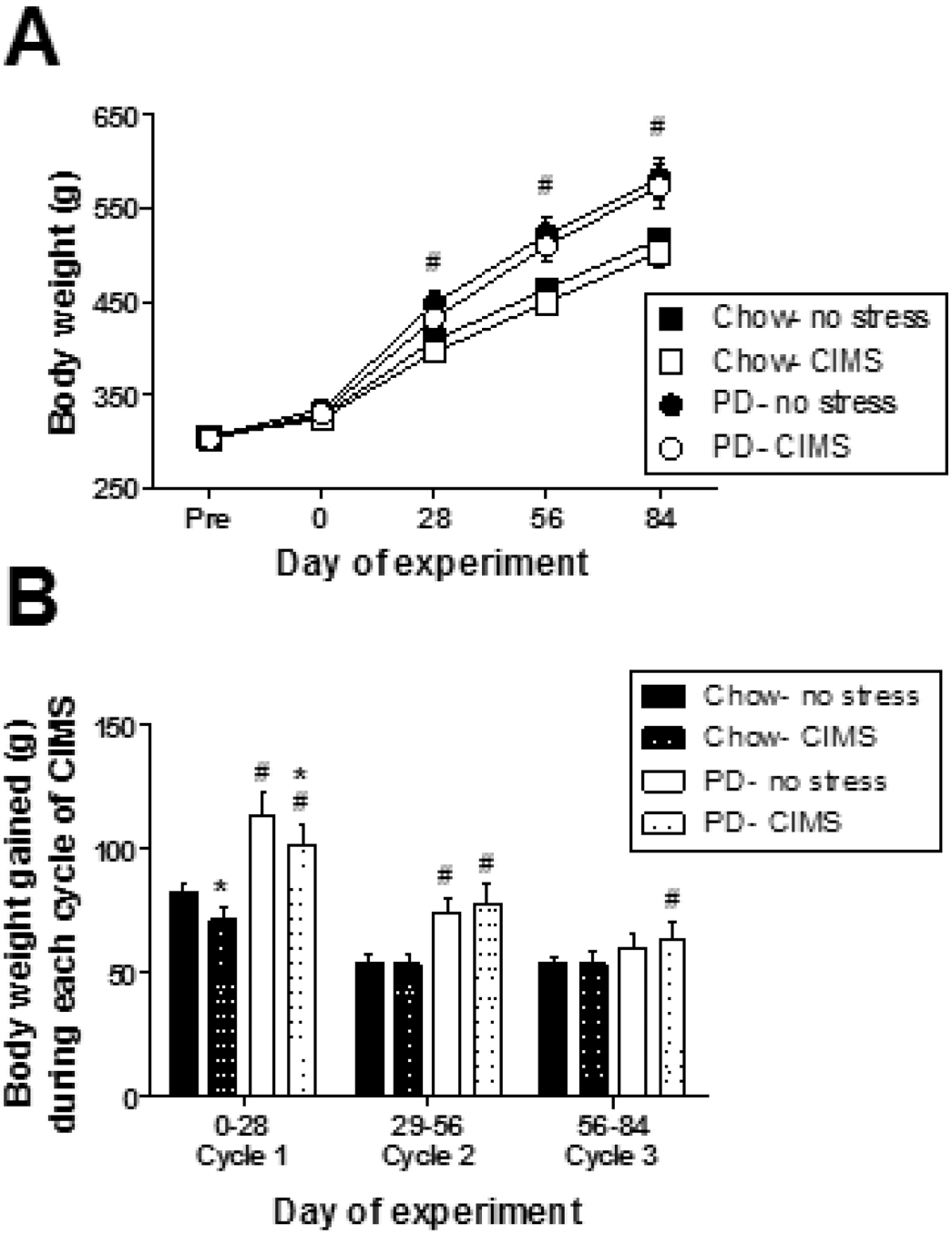

Figure 2.

Palatable diet (PD) increased body weight gain, while chronic intermittent mild stress (CIMS) modestly decreased it during the first cycle of CIMS. (A) Body weight over the duration of the experiment. Pre= pre-study body weight measured on day -4. #$p < 0.05$ denotes both PD-fed groups are greater than their respective chow-fed group. (B) Body weight gained during each of the 3 CIMS cycles. *$p < 0.05$ vs. no stress, #$p < 0.05$ vs. chow. n=12–13/group.

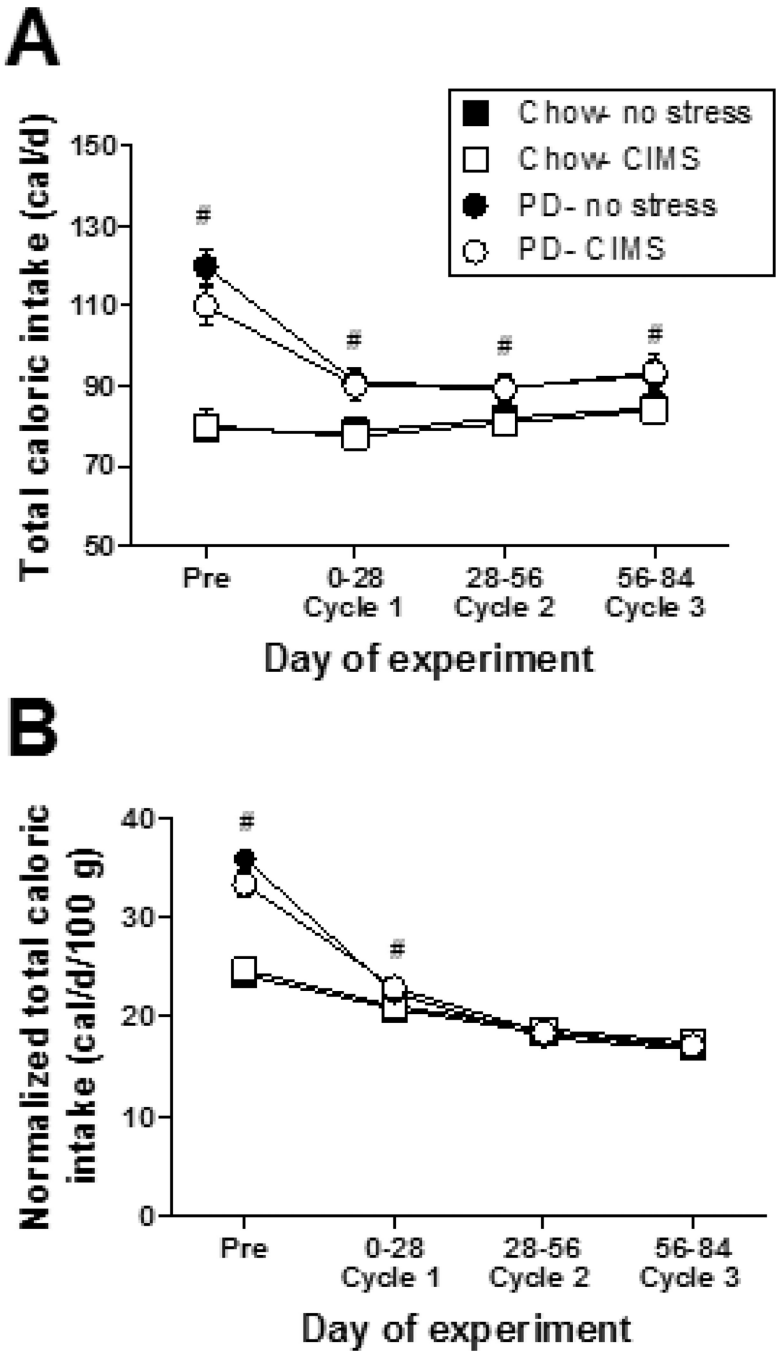

Figure 3.

Total caloric intake was increased by palatable diet (PD), and unaffected by chronic intermittent mild stress (CIMS). (A) Total daily caloric intake from all nutrient sources, and (B) total caloric intake normalized to body weight. Pre= pre-study body weight measured on day -4. #$p < 0.05$ denotes both PD-fed groups are greater than their respective chow-fed group. n=11–13/group. (Chow intake was inadvertently not measured from 1 rat at 1 time point precluding assessment of total caloric intake.)

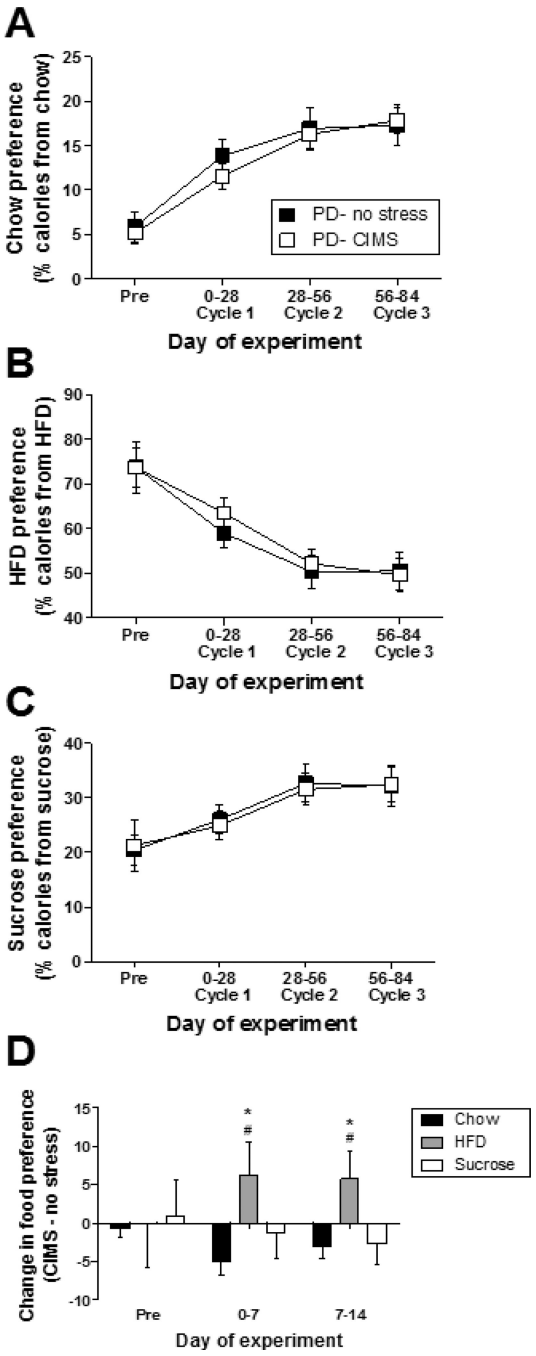

Figure 4.

Chronic intermittent mild stress (CIMS) transiently increased HFD preference during the first 2 weeks of stress. (A) Chow, (B) HFD, and (C) sucrose preference in PD-fed rats (with free access to chow, HFD and sucrose drink) and receiving concomitant CIMS (vs. non-stress controls). Pre= preference during the 4 days prior to CIMS onset (days -4 to 0). (D) The CIMS-induced change in preference for each type of food prior to (Pre) and during the first 2 weeks of the experiment. *$p < 0.05$ vs. both chow and sucrose, #$p < 0.05$ vs. Pre.

n=11–12/group. (Chow intake was inadvertently not measured from 1 rat at 1 time point precluding assessment of food preferences.)

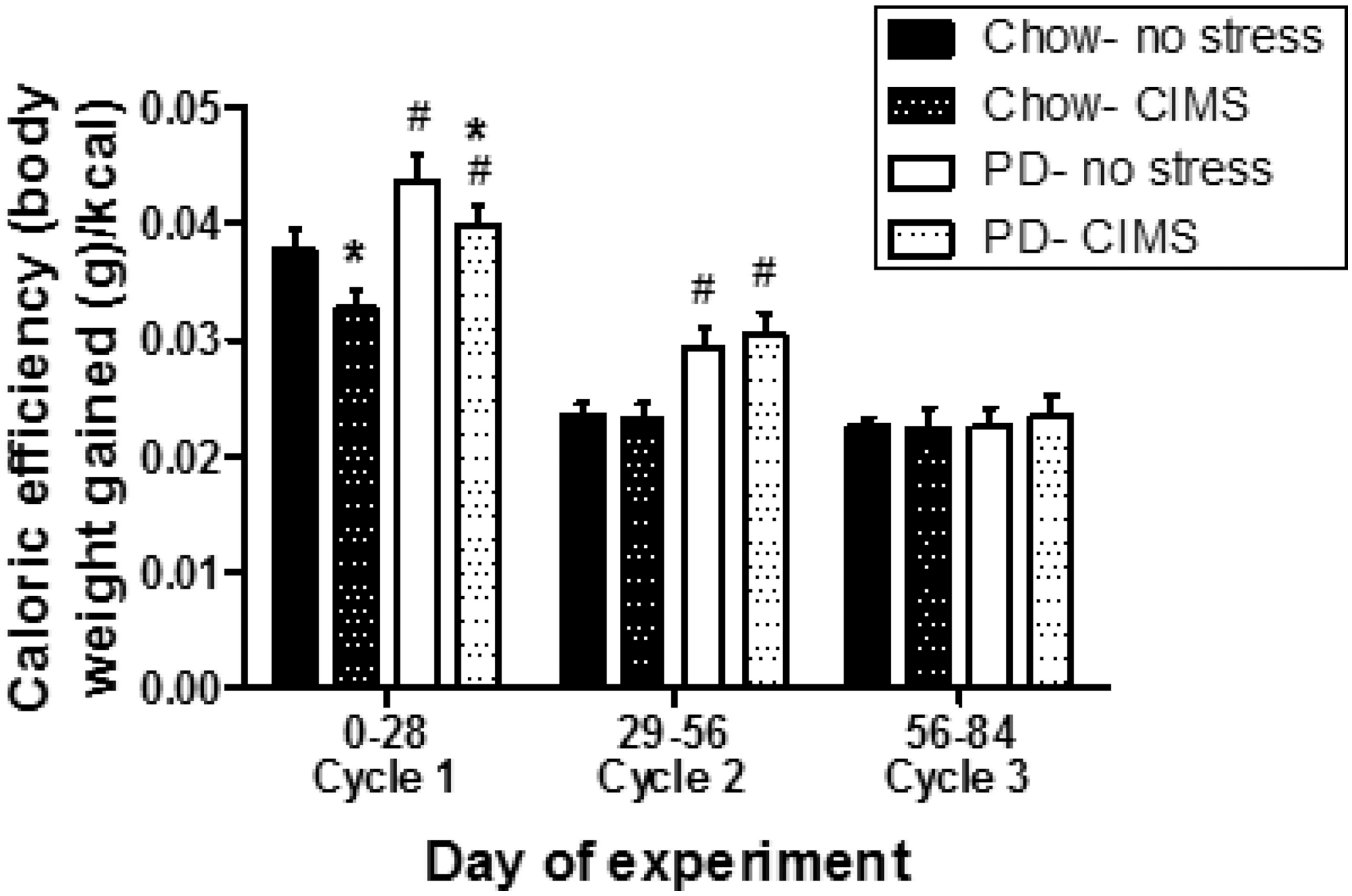

Figure 5.

Palatable diet (PD) increased caloric efficiency, while chronic intermittent mild stress (CIMS) modestly decreased it. PD increased caloric efficiency compared to chow-fed controls during the first 2 cycles of CIMS. In addition, CIMS decreased caloric efficiency compared to no-stress controls during the first cycle of CIMS. *$p < 0.05$ vs. no stress, #$p < 0.05$ vs. chow. n=12–13/group.

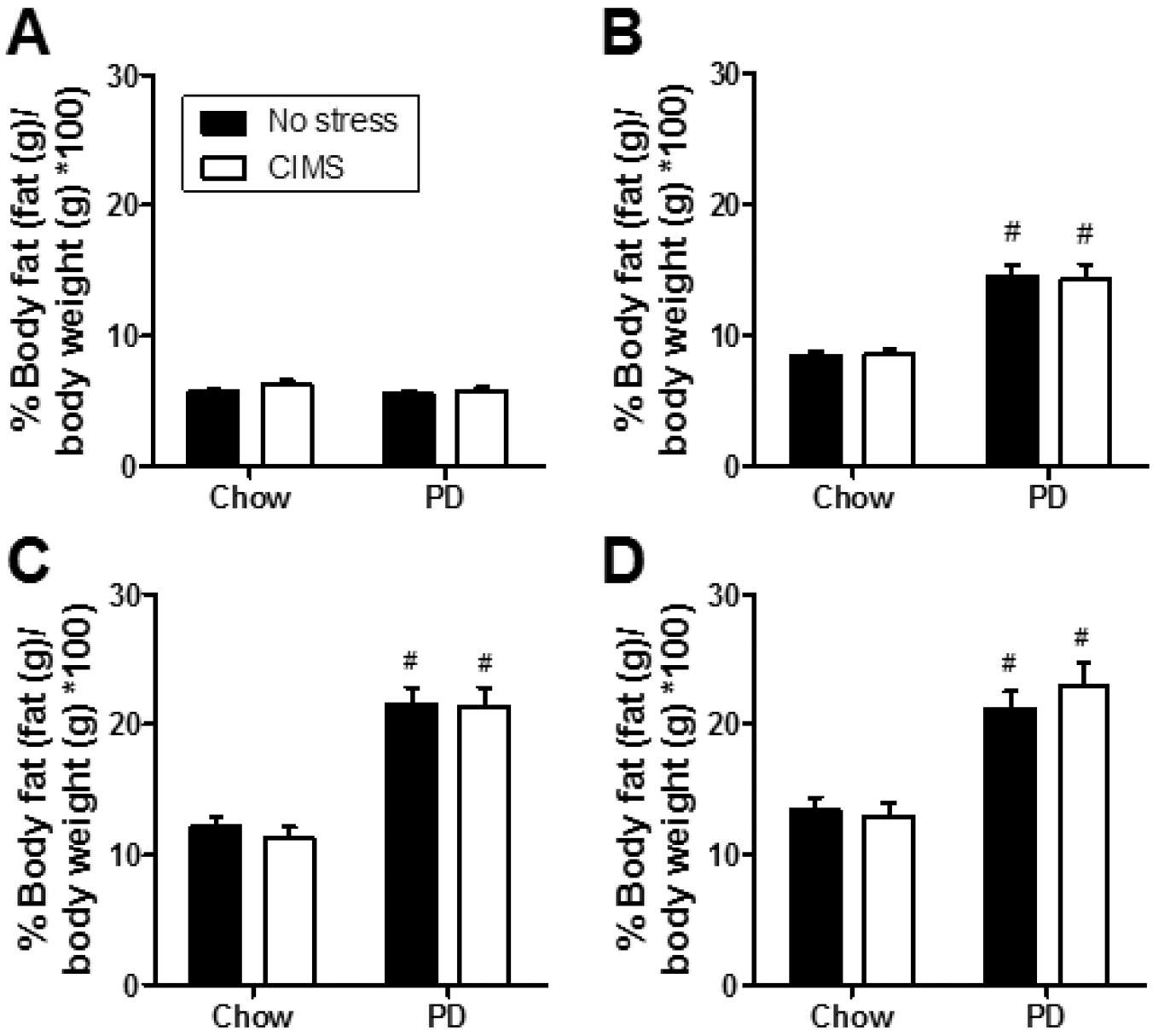

Figure 6.

Palatable diet (PD) increased percent body fat compared to chow-fed controls regardless of chronic intermittent mild stress (CIMS) exposure. (A) Percent body fat prior to study onset (day -4). (B) Percent body fat after the first CIMS cycle (day 23), (C) second CIMS cycle (day 51), and (D) third CIMS cycle (day 79). #$p < 0.05$ vs. chow. n=12–13/group.

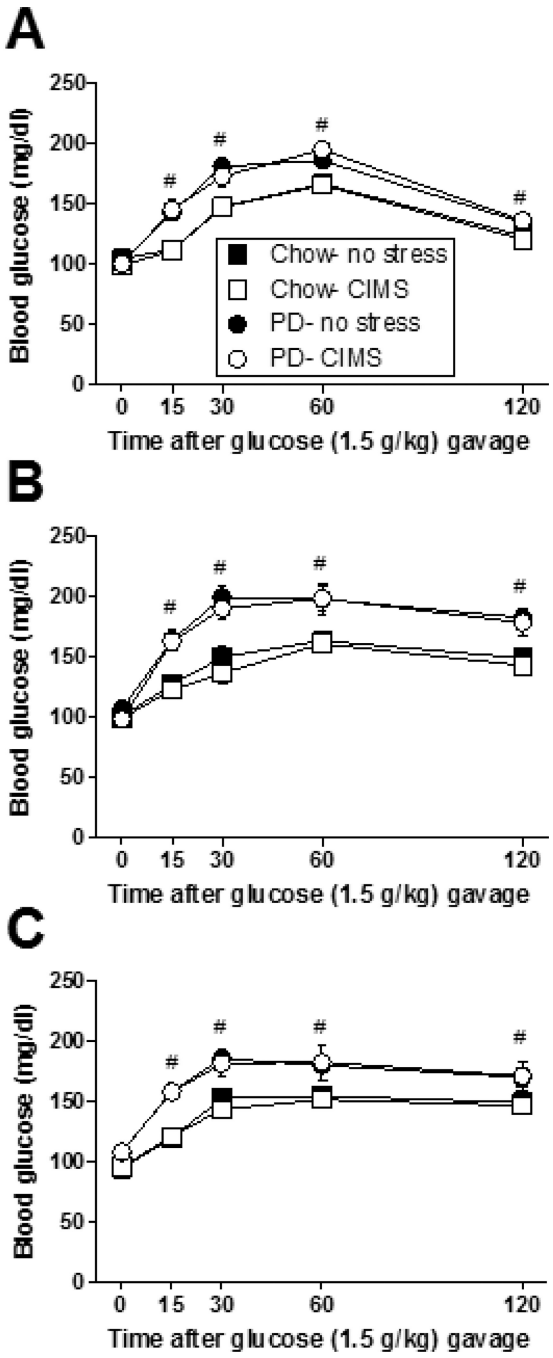

Figure 7.

Palatable diet (PD) impaired glucose tolerance compared to chow-fed controls regardless of chronic intermittent mild stress (CIMS) exposure. (A) Blood glucose during an oral glucose tolerance test given after the first CIMS cycle (day 25), (B) second CIMS cycle (day 53), and (C) third CIMS cycle (day 81). #$p < 0.05$ denotes both PD-fed groups are greater than their respective chow-fed group. n=12–13/group.