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The Effects of Repeated Cycles of Weight Loss and Regain in Rats

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BROWNELL, K. D., M. R. C. GREENWOOD, E. STELLAR AND E. E. SHRAGER. *The effects of repeated cycles of weight loss and regain in rats.* PHYSIOL BEHAV 38(4) 459–464, 1986.—This study examined the metabolic effects of weight cycling, i.e., repeated periods of weight loss followed by regain. There were three groups of adult, male Sprague-Dawley rats: (1) Chow Controls (a normal weight control group fed chow throughout); (2) Obese Controls (animals fed a high-fat diet throughout); and (3) Obese Cycling (obese animals cycled through two bouts of caloric restriction and refeeding). The cycled animals showed significant increases in food efficiency (weight gain/kcal food intake) in the second restriction and refeeding periods compared to the first, i.e., weight loss occurred at half the rate and regain at three times the rate in the second cycle. Several physiological changes were associated with this cycling effect. At the end of the experiment, cycled animals had a four-fold increase in food efficiency compared to obese animals of the same weight who had not cycled. These data suggest that frequent dieting may make subsequent weight loss more difficult. The possible metabolic and health consequences of "yo-yo" dieting are discussed.

Weight cycling Food efficiency Metabolic effects

MOST dieters lose and regain weight many times [14]. Methods for preventing this recidivism are now being studied [9], but little is known about the long-term effects of weight cycling on metabolism and health. The body may respond to dieting as it would to deprivation caused by other factors (e.g., famine) by increasing food efficiency, i.e., by maximizing weight, body fat, lean body mass, or some related factor given the available food. Dieting may enhance efficiency, thereby making subsequent dieting more difficult.

Humans who lose and regain repeatedly ("yo-yo" dieters) may develop this dieting-induced food efficiency that inhibits weight loss and promotes regain. This is an important problem considering the current preoccupation with weight loss and dieting [18] and the possible effects of weight cycling on health. A Gallup poll in November, 1985 found that 31% of American women ages 19–39 diet *at least once a month*, and that 16% consider themselves perpetual dieters. It is clear that more information is needed on the effects of repeated cycles of loss and regain.

Studies with animals have shown consistent metabolic effects of a single cycle of restriction and refeeding. The data point to increased metabolic efficiency in both normal weight and obese animals [4, 6, 7, 20, 27, 29, 31, 34]. A study by Bjorntorp and Yang [4], for example, found a five-fold increase in food efficiency in previously fasted rats in the 8 days following a 25% loss in body weight. That is, the caloric maintenance requirements per gram of body weight were substantially reduced by previous dieting experience. Fur-

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thermore, animals made obese with a high fat diet can maintain their obese weight when switched to a chow diet, even when eating calories equivalent to control animals of normal weight [10, 30, 31].

Studies of loss and regain in animals suggest possible mechanisms for the increased efficiency. Changes include increased activity of lipoprotein lipase [13,15], altered body composition [4,34], decreased metabolic rate [6,35], lowered heat increment in response to food [7], and changes in small intestine enzymes [2, 3, 20, 34], the flux of energy from plasma to peripheral tissue [2, 3, 5], and adipose tissue morphology [11,28].

Far less is known about loss and regain in humans. It is clear that large differences exist among obese persons in the energy required for weight maintenance and loss [8,14]. The oft-voiced complaint of some people who struggle with their weight, that they remain heavy despite low intake, has been substantiated with metabolic studies. Leibel and Hirsch [24], for example, studied reduced obese persons who had lost an average of 52 kg. Their energy requirement was 25% less than expected for their body size, and although they still weighed 60% more than matched controls, they required less energy for maintenance of body weight. It has been suggested that a history of repeated dieting is a poor prognostic sign for treatment [17], although this has not been studied extensively. This resistance to weight loss could reflect the putative metabolic cause of obesity, or could be induced by dieting itself, as suggested by the animal studies cited above.

The importance of this weight cycling issue may not be confined to obese persons because dieting is such a common practice in the general public. Many individuals in the range of normal weight lose and regain repeatedly, even though the fluctuations involve only a few pounds. Some persons who maintain normal weight do so by eating very little, often less than 1,000 calories per day [24]. Some groups, by virtue of avocation or profession, keep their weights chronically low (dancers, models, figure skaters, runners) or lose weight and regain repeatedly (wrestlers).

This study was designed to develop an animal model to test the behavioral and metabolic effects of weight cycling. We hypothesized that energy efficiency would increase as animals cycled through periods of restriction and regain.

METHOD

Twenty-eight male, Sprague-Dawley rats (Holtzman, Madison, WI) were acquired at 150 days of age and were housed individually in suspended cages in a temperature controlled room on a 10:14 hr light-dark cycle (lights on at 08:00 hr). They were acclimated to these conditions for three days and were supplied ad lib with Purina Lab Chow in pellets. Food was supplied in double jars. Most of the spillage was recovered in the larger outside jar; additional spillage under the hanging cages was routinely quantitated. Body weight and food consumption were recorded daily at 10:00 hr except on weekends. Tap water was supplied ad lib.

For the animals receiving a high fat diet, a semi-solid diet mixture (BioServ Diet No. 1352, Frenchtown, NJ) was given ad lib. This mixuture was supplemented with protein and vitamin and mineral supplements to avoid protein deprivation. The composition of the diet was 18% protein, 63% fat, and 7% carbohydrate.

Animals were randomly assigned to three conditions: (1) *Chow Controls:* ad lib access to chow throughout the experiment; (2) *Obese Controls:* ad lib access to the high fat diet throughout the experiment; (3) *Obese Cycling:* animals were allowed ad lib access to the high fat diet until becoming obese and then were restricted and refed for two cycles.

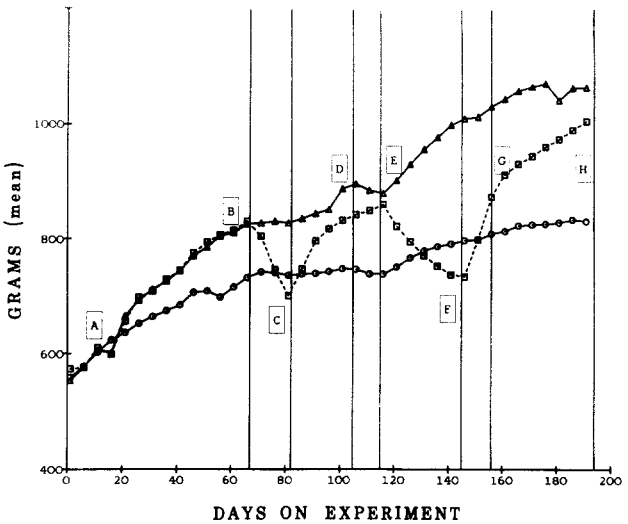

FIG. 1. Body weight changes in Chow Controls (Group 1), Obese Controls (Group 2), and Obese Cycling animals (Group 3), at the beginning of the experiment (A), beginning of the first restriction (B), end of the first weight loss period (C), point of weight regain to prediet weight (D), initiation of the second diet cycle (E), end of the second weight loss period (F), point of weight regain to prediet weight (G), and end of experiment (H).

All animals were given chow for 34 days to begin the experiment. At this point, the three groups to which animals had been randomly assigned did not differ statistically in body weight or rate of weight gain. The Obese Controls and Obese Cycling groups were then given the high fat diet ad lib for 67 days at which point they were 14.12% heavier than the Chow Controls. Then the Obese Cycling group began the two cycles of restriction and refeeding. During the restriction, the Obese Cycling animals were allowed 50% (18 g/day) of the average intake of the chow consumed by the Chow Controls. During the refeeding phases, the rats resumed ad lib access to the high fat diet. For the first cycle, the animals were restricted until they reached the weight of the Chow Controls, and then were allowed to regain to the weight of the Obese Controls. Weight loss in the second cycle was equated to the loss of the first cycle, and then the animals regained to their prediet weight and were allowed to regain to the weight of the Obese Controls by the end of the experiment.

During these restrictions, an attempt was made to mimic the human dieting experience. The animals were switched from the palatable high-fat diet to the bland but nutritious chow, and were given 50% what the normal weight animals were eating. In our experience, human dieters typically switch to nutritious foods with low to moderate calorie density, and cut their intake to approximately 1/2 that of the normal weight people of the same age and sex.

Food efficiency was estimated as the ratio of weight change in a given period to the amount of energy consumed. At sacrifice, all animals were two hours post prandial. Right and left epididymal and retroperitoneal fat pads were dissected and inguinal pads were sampled. The right fat pads

TABLE 1

BODY WEIGHT CHANGE, FOOD EFFICIENCY, AND BODY COMPOSITION (MEAN ± S.E.M)

	Chow Control (G1)	Obese Control (G2)	Obese Cycling (G3)	G1 vs. G2	G1 vs. G3	G2 vs. G3
Body Weight and Food Efficiency						
Weight at (C)	737.0 ± 23.1	841.1 ± 41.2	701.7 ± 19.1	ns	ns	*
% Weight Change at (C)	0.2 ± 0.63	−0.2 ± 0.54	−16.1 ± 0.78	ns	†	†
Weight Gain at (D)	7.0 ± 3.7	52.8 ± 8.9	135.1 ± 11.0	†	†	†
Food Efficiency at (D)	—	0.0205 ± 0.009	0.0411 ± 0.007	—	—	†
Weight at (E)	739.6 ± 25.6	881.3 ± 45.0	861.5 ± 32.0	*	*	ns
Food Efficiency at (E)	—	0.0051 ± 0.006	0.0173 ± 0.004	—	—	ns
Weight at (F)	792.4 ± 28.1	1008.1 ± 55.6	724.0 ± 23.4	*	ns	†
% Weight Change at (F)	6.9 ± 1.05	14.6 ± 0.54	−15.6 ± 0.83	†	†	†
Weight at (G)	807.9 ± 30.3	1020 ± 57.1	843.0 ± 26.2	*	ns	*
Weight Gain at (G)	15.5 ± 3.4	11.9 ± 3.1	119.0 ± 4.8	ns	†	†
Food Efficiency at (G)	—	0.0094 ± 0.008	0.0627 ± 0.005	—	—	†
Weight at (H)	828.4 ± 36.6	1055 ± 65	1002 ± 39	*	*	ns
Food Efficiency at (H)	—	0.0052 ± 0.004	0.0218 ± 0.002	—	—	†
Body Composition						
Percent Fat	19.3 ± 2.1	33.1 ± 3.3	28.2 ± 1.9	*	*	ns
Percent Protein	16.9 ± 1.3	13.2 ± 0.4	14.9 ± 1.0	ns	ns	ns
Percent Water	54.1 ± 2.0	43.9 ± 2.6	45.2 ± 2.3	*	*	ns

*$0.05>p>0.001$.
†$p<0.001$.

were sampled for determination of cellularity. The left pads were sampled for cellularity and the remainder processed for LPL determinations. Cellularity was determined by electronic counting of osmium-fixed cells, and lipids were determined gravimetrically as described previously [16]. Serum immunoreactive insulin was determined by radio-immunoassay using the back tritration method of Wright *et al.* [36] and pure rat insulin standard.

Body composition was determined by carcass analysis. The carcasses were weighed and then autoclaved under pressure (20 lb/m²) at 120 degrees for 1 hour. The carcass was homogenized with an equal weight of water in a polytron homogenizer. Aliquots were weighed for determination, lipid was determined according to Folch [12], and moisture was considered by drying to constant weight at 60 degrees C. The protein contents were calculated by multiplying the grams of nitrogen by 6.25. Analyses of variance and slope analyses were used for statistical comparisons.

RESULTS

The results which follow make reference to periods of loss and gain (denoted by upper case letters A–H) displayed in Fig. 1 and explained in the legend for that figure. There were large and significant differences in the weight loss and gain patterns of the Obese Cycling animals in their first and second cycles (Fig. 1, Table 1). In the first restriction, these animals attained the weight of the Chow Controls by reducing 131 g. In the second restriction, weight loss was controlled to equal that of the first restriction; the mean change was 133 g. This loss required 21 days in the first cycle and 46 days the second. Slope analysis indicated a significantly slower loss on the second cycle compared to the first [X slope (B–C)$=-10.9$ vs. X (E–F)$=-4.63$, $p<0.0001$].

Changes in weight patterns were even more pronounced during refeeding. Forty-six days were required for the Obese Cycling group to regain to the weight of the Obese Controls

(average gain=131 g) in the first refeeding. To regain the same weight in the second refeeding required only 14 days. Slope analysis revealed significantly more rapid weight gain in the second refeeding [X slope (C–D)=5.89 vs. X (F–G)=12.13, $p<0.0001$].

Food efficiency changed significantly in the Obese Cycling group from the first to the second cycles. Although the daily food intake was the same during both restrictions (18 g/day), weight loss was less rapid in the second cycle. Therefore, food efficiency was significantly greater in the second cycle [FE slope (B–C)=−0.11 vs. FE (D–F)=−0.04, $p<0.0005$]. Efficiency also increased in the second refeeding (Fig. 2). In the second refeeding stage, food efficiency (g body weight/g food) was 0.0627 compared to 0.0411 in the first refeeding ($p<0.0001$). For the last 20 days of the experiment, the Obese Cycling and Obese Control groups were maintaining the same weights, but food efficiencies were 0.02 and 0.005, respectively ($p<0.002$). At the very end of the experiment (point H, Fig. 1), the food efficiency figures for these two groups were 0.022 and 0.0052, respectively ($p<0.001$). There was a four-fold increase in food efficiency in the Obese Cycling group.

Because basal metabolic rate and metabolic efficiency change with age, it is important to isolate the effects of age and diet history in the Obese Cycling group. This was done by using the Obese Controls as age controls. Food efficiency was calculated for the Obese Controls for the same periods that the Obese Cycling animals were in the loss/gain cycles. Figure 2 shows the food efficiency of both groups during the first and second refeeding periods. There was a nonsignificant decrease in the Obese Controls over time, while the Obese Cycling group had a significant increase.

Metabolic and weight data are presented in Tables 1 and 2. Compared to the Chow Controls, the two obese groups had significantly higher percent body fat and lower percent body water. There were no significant differences between the two obese groups for these measures and there were no differences among the three groups in body protein or plasma insulin at the end of the experiment.

Compared to the Chow Controls, both obese groups had significantly increased number of fat cells and increased pad weight in the epididymal, retroperitoneal, and inguinal pads. There were no significant differences among the groups for cell size in the three pads except that the Obese Cycling group had greater cell number than the Chow Controls in the retroperitoneal pad. LPL activity, expressed as LPL per cell, was increased significantly in the retroperitoneal pad of the Obese Cycling group, but was not significantly different in the epididymal pad, suggesting a possible regional response to cycling.

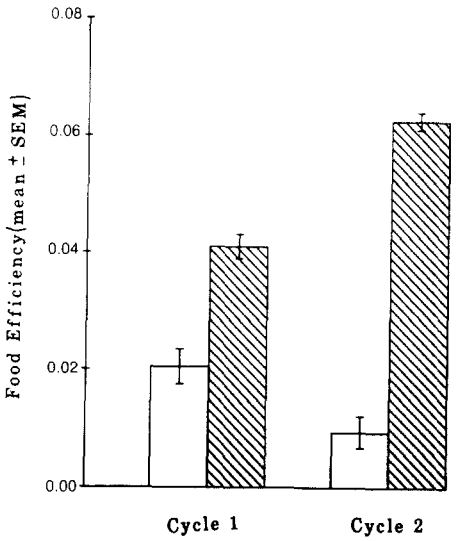

FIG. 2. Food efficiency for Obese Controls and Obese Cycling animals during the two regain periods. Cycle 1 is the period C–D on Fig. 1 and Cycle 2 is the period F–G. Open bars are Obese Controls and crosshatched bars are Obese Cycling animals.

DISCUSSION

These results demonstrate strong metabolic effects of cycles of weight loss and regain. This phenomenon was apparent in changes over time in cycled animals and in the comparison of these animals with the Obese Controls. After one cycle of loss and regain, the animals showed significant alterations in weight loss and regain patterns. At the end of the experiment, the Obese Cycling animals were at the same body weight as the Obese Controls, but their food efficiency was increased significantly.

Other studies have shown similar effects in both obese and lean animals during a single bout of restriction and refeeding [4, 6, 7, 27, 29–31, 34]. Our results suggest that the effect not only endures with subsequent cycles but that energy efficiency increases further. Considering that the single cycle effect has been demonstrated in both obese and lean animals, it will be important to test lean animals for the effects of multiple cycles.

The magnitude of these changes in food efficiency is noteworthy. The cycled animals required more than twice the time (21 vs. 46 days) to lose the same amount of weight during the second restriction compared to the first (food efficiency was increased 142%). One-third the time (10 vs. 29 days) was required to regain weight in the second refeeding. Food intake increased 25% and efficiency 52% in the second refeeding. The difference did not appear to be due to age, as efficiency decreased slightly over time in the age-matched Obese Controls while it increased significantly in the cycled animals.

Our data on body composition and fat cell morphology are consistent with those from other studies on the effects of dietary obesity [30]. The two obese groups in our study had increased body fat and increased fat cell number in two of the three fat pads studied and increased cell size in one depot. They also had increased LPL activity per cell in the retroperitoneal pad. The lack of differences in the Obese Cycling and Obese Control groups indicates that cycling does not prevent the hypercellular response and the increase in body fat produced by the high fat diet. Although there were no differences in final body protein content, this does not exclude the possibility that significant losses of lean body mass occurred during the cycle. It is possible that depletion of body protein stores is a significant component of the response to cycling.

The fact that the terminal metabolic measures taken in this study did not reveal consistent differences between the Obese Control and Obese Cycling groups might suggest that increased energy efficiency is not mediated by either changes in body composition or fat cell morphology. However, since the Obese Cycling group was still gaining weight

TABLE 2

ADIPOSE TISSUE CELLULARITY, LPL ACTIVITY, AND INSULIN ACTIVITY (MEAN ± S.E.M.)

	Chow Control (G1)	Obese Control (G2)	Obese Cycling (G3)	G1 vs. G2	G1 vs. G3	G2 vs. G3
Retroperitoneal Pad						
Pad Weight (g)	7.12 ± 1.25	26.42 ± 2.65	26.42 ± 2.52	†	†	ns
Cell Number ($\times 10^6$)	2.48 ± 0.49	7.98 ± 1.41	6.74 ± 1.15	*	*	ns
Cell Size	0.022 ± 0.001	0.027 ± 0.004	0.032 ± 0.003	ns	*	ns
LPL/Cell	0.876 ± 0.092	1.343 ± 0.263	1.259 ± 0.130	ns	*	ns
Epididymal Pad						
Pad Weight (g)	8.9 ± 1.3	16.8 ± 1.1	17.3 ± 0.86	†	†	ns
Cell Number ($\times 10^6$)	2.53 ± 0.35	4.56 ± 0.27	5.15 ± 0.30	*	*	ns
Cell Size	0.026 ± 0.002	0.026 ± 0.002	0.025 ± 0.002	ns	ns	ns
LPL/Cell	1.71 ± 0.30	1.67 ± 0.11	1.66 ± 0.21	ns	ns	ns
Inguinal Pad (Cell Size)	0.0189 ± 0.002	0.0219 ± 0.001	0.0227 ± 0.001	ns	ns	ns
Isulin (μU/ml)	91.6 13.8	95.7 17.7	93.7 14.5	ns	ns	ns

*$0.05 > p > 0.001$.
†$p < 0.001$.

when the terminal measures were taken, the possibility exists that eventually they might have shown increased adiposity. It will be important in future studies to examine these and other metabolic factors (e.g., metabolic rate, thermogenesis) throughout the cycles to evaluate effects during dynamic stages of cycling.

It is possible to view these changes in rate of weight change and metabolic efficiency as an adaptive response to cycles of energy deprivation. An organism repeatedly deprived of food would increase the chance of survival by conserving energy during scarcity and by converting food to body stores more efficiently when food is available. With repeated cycles, the organism might be expected to lose more slowly and regain more rapidly.

It is possible only to speculate about the extrapolation of our results with animals to the effects of weight cycling on humans. One important aspect of this issue with humans may be the effects of weight cycling on health. For example, several of the coronary risk factors in humans, notably blood pressure, lipids and lipoproteins, and insulin resistance change as weight increases or decreases [8, 14, 32]. It is possible that weight loss and regain, even when there is no net change in weight, might produce harmful effects if the associated risk factors respond in a negative fashion. Data from the Framingham Study [1], for example, indicate that rises in blood pressure during weight regain are greater than the reductions with the same degree of weight loss.

Changes in fat distribution may also be important. Individuals with lower body obesity (female or gynoid type—fat distributed below the waist) are at less risk for hypertension and impaired glucose tolerance compared to those with upper body obesity [19, 21, 37]. Krotkiewski *et al.* [21] estimated that as much as 20 pounds of excess fat can be tolerated in the lower body without excess risk but that the same amount in the upper body is associated with increased mortality from coronary disease. Weight cycling, therefore, could increase risk if the fat that is lost and then regained is redistributed and the proportion of fat in the upper body increases. This possibility is suggested by recent work showing that receptors in adipose tissue promote fat deposition more readily in the upper than the lower body [25,26].

Our findings, along with those from studies on single cycles of loss and regain, show strong metabolic effects of the "yo-yo" pattern so common to human dieters. These metabolic effects, combined with possible health risks, suggest the need for more research on weight cycling in both humans and animals.

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