The role of a high-sugar refined diet on food and energy intake, body weight, exercise, and motivation in rats

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Consumption of foods made from highly processed and refined ingredients has been identified as one of the leading causes of poor physical health and disease, such as obesity, diabetes, metabolic syndrome, cancer, degenerative disease, cardiovascular disease, and autoimmune disease [1]. In addition to its effects on physical health, diet also plays a major role in mood, cognition, and psychological wellbeing [2]. We previously reported research from our lab showing deficits in attention and motivation in rats consuming a refined, purified (REF) high-sugar diet compared to a control (CON) diet [3][4].

Here we report interesting effects of the REF diet on body weight and food consumption in response to discontinuation of behavioral testing. We also discuss unexpected effects of a REF diet on wheel running activity and body weight. Finally, switching from a REF to a CON diet for 5 weeks improved motivational deficits induced by chronic consumption of the REF diet. These results suggest that highly processed, high-sugar diets dysregulate energy homeostasis that can be reversed with a sufficiently long switch to a healthier diet.

How does eating refined food affect food consumption and weight?

An outbred strain of female rats (Long-Evans, Harlan) was used in our study (group *n* = 16). One group was fed a commercial purified REF diet (Research Diets D12450B), while a second group was fed a CON chow diet (LabDiets5001). Diets (Table 1) were chosen to mimic real-world human diets consisting of highly processed (REF diet) or low-processed (CON diet) ingredients.

Table 1

CON (Chow) diet
Ground corn, dehulled soybean meal, dried beet pulp, fish meal, ground oats, brewers dried yeast, cane molasses, dehydrated alfalfa meal, dried whey, wheat germ, porcine animal fat, porcine meat meal, wheat middlings, salt, calcium carbonate, DL-methionine, choline chloride, cholecalciferol, vitamin A acetate, folic acid, menadione dimethylpyrimidinol bisulfite (source of vitamin K), pyridoxine hydrochloride, thiamin mononitrate, nicotinic acid, calcium pantothenate, dl-alpha tocophyryl acetate, vitamin B12 supplement, riboflavin, ferrous sulfate, manganous oxide, zinc oxide, ferrous carbonate, copper sulfate, zinc sulfate, calcium iodate, cobalt carbonate, sodium selenite.

REF diet
Sucrose, corn starch, casein, cellulose, maltodextrin, soybean oil, lard, potassium citrate, dicalcium phosphate, calcium carbonate, vitamin mix, choline bitartrate, FD&C Yellow Dye #5.

	Chow Diet	Refined Diets
Protein	28.5%	20%
Carbohydrate	58%	70%
Fat	13.5%	10%
Metabolizable energy Kcal/gm	3.02	3.85

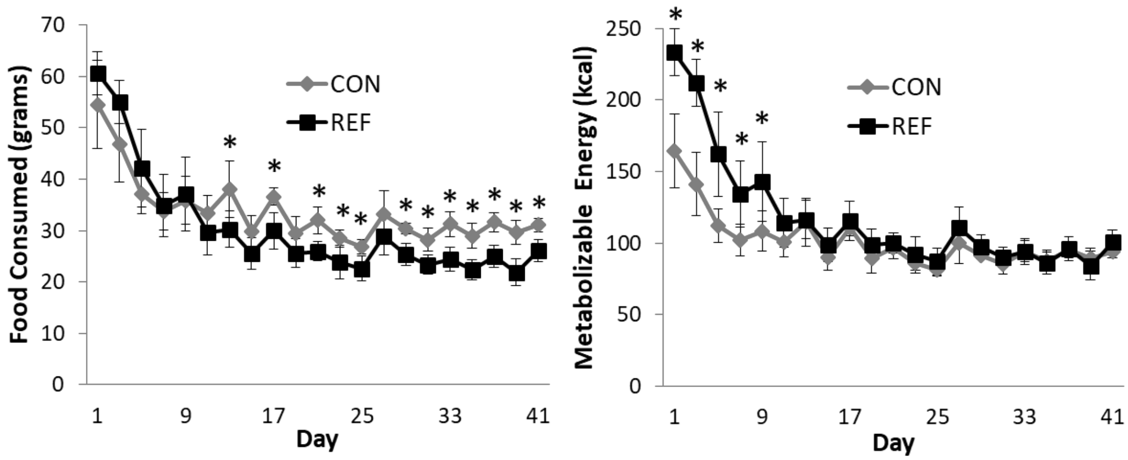
Rats consuming the REF diet ad lib for two months gained significantly more fat mass (on the left in Figure 1) compared to the CON diet (on the right in Figure 1, see [4] for further details).

Figure 1. The rat on the left consumed a REF diet while the rat on the right consumed a CON diet for 41 days prior to when this photo was taken. The photo is representative of the physical differences between the REF and the CON diet.

Prior to ad lib consumption, both groups had been on a restricted feed schedule (to 85% of free feeding weight) for the CON diet to motivate performance in a behavioral test of attention. At the completion of training, rats were given ad lib access to either the CON or REF diet. Figure 2 shows that both groups of rats did not start out consuming different amounts of food, but by day 13, rats on the CON diet consumed more food than rats on the REF diet. A two-way Repeated Measures (RM) Analysis of Variance (ANOVA) conducted on food consumed found a Diet x Day Interaction, $F(20, 280) = 3.50$, $p < 0.001$. Post-hoc analyses revealed significant group differences ($p < 0.05$) on days 13, 17, 21-25, and 29-41. Given the higher energy density of the REF diet, these levels of food consumption resulted in rats on the REF diet consuming a greater amount of metabolizable energy during the first 9 days on the diet, followed by similar levels of energy intake thereafter (Figure 2, right panel); Diet x Day Interaction $F(20, 280) = 6.74$, $p < 0.001$. Post-hoc analyses revealed significant group differences ($p < 0.05$) on days 1-9.

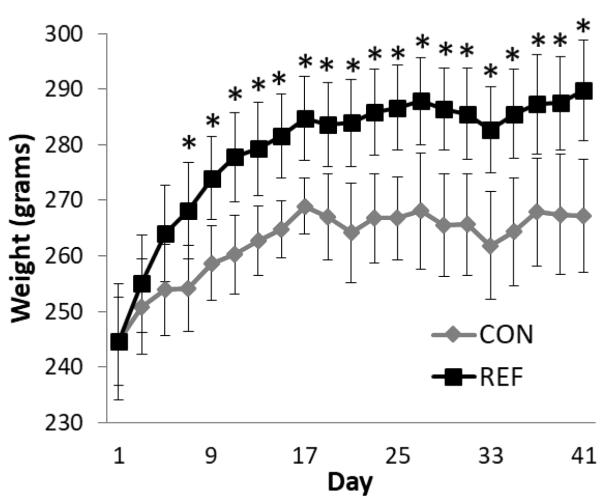
DOI: 10.15310/2334-3591.1084

Figure 2. Mean food consumed (left panel) and metabolizable energy consumed (right panel) by rats consuming a REF or CON diet. Error bars indicate 95% Confidence Intervals. Asterisks indicate significant group differences at the p < 0.05 level.



The greater energy consumption by rats on the REF diet during the first 9 days led to an increased weight gain as compared to rats that had normal weight gain consuming the CON diet (Figure 3). Rats on the REF diet became significantly heavier by day 7 of the diet, as supported by a Day x Diet Interaction, $F(20, 600) = 5.38$, $p < 0.001$. After day 17, weights were for the most part stabilized.

Figure 3. Mean weight gain in rats consuming a REF or CON diet. Error bars indicate 95% Confidence Intervals. Asterisks indicate significant group differences at the p < 0.05 level.



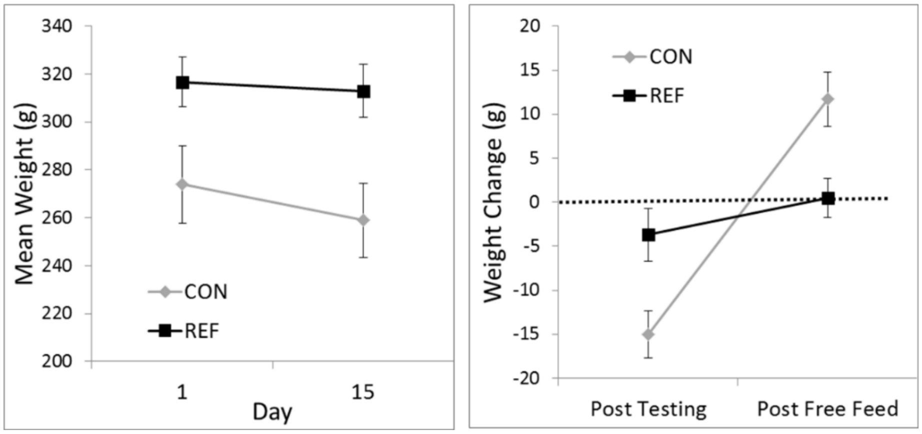
Effects on food consumption of withdrawal of a sucrose reward

After the initial exposure to the diets as described above, rats received 6 months of behavioral testing on an attention task in which they could earn a sucrose reward for pressing a lever after the onset of a cue. In that study, REF diet caused impairments in attention and behavioral control (4).

Following the attention task, rats stopped receiving behavioral training with sucrose reinforcement, but were maintained on restricted feed such that each cage of pair housed rats received 25g daily of their respective diets for 15 days. Unexpectedly, this discontinuation of daily access to a small sucrose reward affected food consumption and weight maintenance in the two diet groups differently. Body weight decreased more in rats on the CON diet than in rats on the REF diet, as shown in the left panel of Figure 4, and revealed by a Diet x Day interaction, $F(1, 30) = 30.19$, $p < 0.01$. While rats on the REF diet also lost some weight, $F(1, 30) = 6.42$, $p = 0.017$, weight loss was greater for rats on the CON diet, $F(1, 30) = 106.15$, $p < 0.0001$. An analysis of weight change showed that CON rats lost significantly more weight than REF rats, $t(30) = 5.49$, $p < 0.01$. The “Post Testing” data in the right panel shows the difference in weight from day 1 to day 15 following discontinuation of sucrose reward. After day 15, rats were placed back on ad lib feed of their respective diets (REF or CON), which resulted in the CON rats regaining all of their lost weight over the course of a week (Figure 4, right panel, “Post-free feed”). This was possibly due to insufficient nutrition delivered by the 12.5 g of food daily to rats on the CON diet, which was corrected when placed on ad lib feeding. These conclusions were supported by a Diet x Time (Pre and Post) Interaction, $F(1, 30) = 30.19$, $p < 0.001$, with the caveat that the weight change post testing took place across the span of 15 days, while the weight change that took place post free feeding took place across the span of 8 days. We discuss the implications of this difference in the General Discussion.

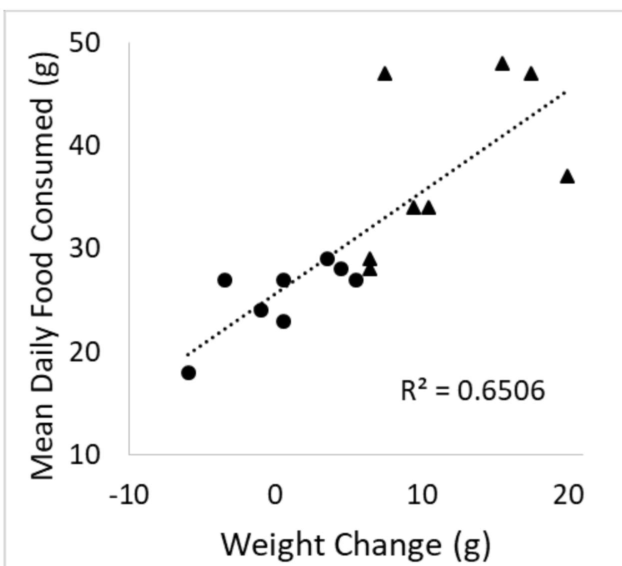
DOI: 10.15310/2334-3591.1084

Figure 4. Effect of discontinuation of daily access to a small sucrose reward on total weight (left panel) and change in weight (right panel) on days 1 and 15 after discontinuation to training with sucrose reinforcement. "Post Testing" shows the mean difference in weight between days 1 and 15, while "Post Free Feed" shows the change in weight over the week following day 15, after ad lib access to their respective diets (REF and CON). Error bars indicate 95% Confidence Intervals.



As expected, the amount of individual weight gain was positively correlated with the amount of food consumed following return to unrestricted feeding (Figure 5), $r^2 = 0.65$, $p < 0.001$.

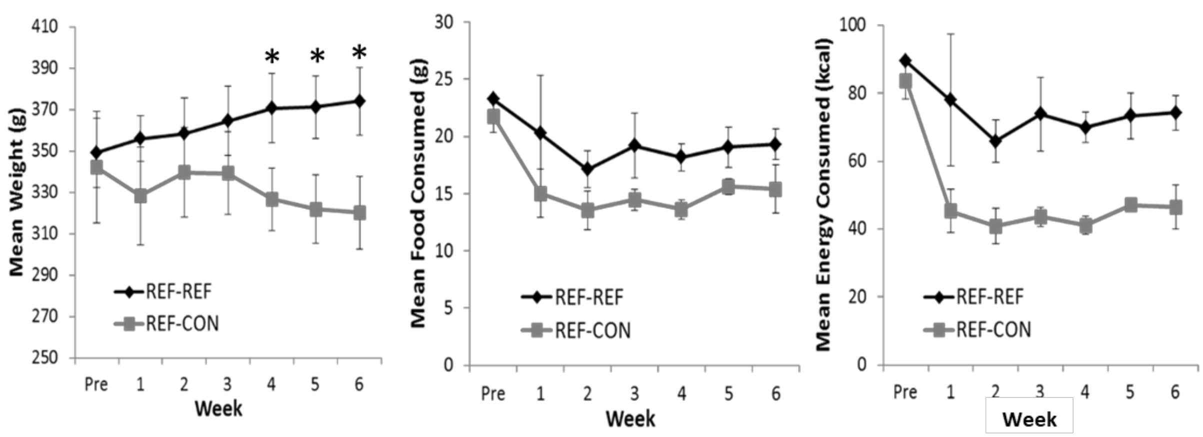
Figure 5. Correlation between mean daily food consumed per cage and body weight change per rat after being placed back on free feed. Triangles depict data from CON rats, circles depict data from REF rats. Rats that consumed the most food experienced the greatest weight gain.



Relationship between activity and diet quality.

Following nine months after the data (above) were collected, 8 rats that had been consuming a REF diet were individually housed for a 5-week period in home cages that contained a running wheel. Four of the rats remained on the REF diet while the other 4 were switched to a CON diet during this 5-week period. Rats that had been switched to a CON diet consumed less food than rats that remained on the REF diet (Figure 6, center panel), as revealed by a main effect of Diet, $F(1, 6) = 32.05$, $p < 0.01$. They also consumed less energy (Figure 6, right panel), $F(1, 6) = 66.75$, $p < 0.001$. Weight differences between the CON and REF groups diverged from each other (Figure 6, left panel), as supported by a Week by Diet interaction, $F(5, 30) = 14.52$, $p < 0.001$. Post hoc analyses revealed significantly lower weight in the CON rats than REF rats on Weeks 4-6, *p*s < 0.01. Compared to prior to placement in the running wheel cages, by week 6 rats that remained on the REF diet ate less total food (center panel), $F(1, 6) = 19.84$, $p < 0.01$, and consumed less energy (right panel) $F(1, 6) = 24.77$, $p < 0.01$. By week 6, however, rats on the REF diet continued to consume more food, $F(1, 6) = 9.22$, $p < 0.05$, and energy, $F(1, 6) = 43.57$, $p < 0.001$, than the rats that had been switched to the CON diet. Rats that were switched to a CON diet consumed more food, $F(1, 6) = 51.01$, $p < 0.001$, and energy, $F(1, 6) = 147.58$, $p < 0.001$, and did not show significant weight loss $F(1, 6) = 5.66$, $p = 0.055$ from Pre to week 6. Interestingly, unlike rats switched to the CON diet, rats that remained on the REF diet actually *gained* weight during the 5-week period (left panel), $F(1, 6) = 7.32$, $p < 0.035$ *despite consuming less food and energy from Pre to week 6,* $F(1, 6) = 19.84$, $p < 0.01$ *and* $F(1, 6) = 24.77$, $p < 0.01$.

Figure 6. Mean weight (left panel), food consumed (center panel) and energy consumed (right panel) by rats that continued to consume a REF diet (Group REF-REF) or that had been switched to consuming a CON diet after chronic consumption of a REF diet (Group REF-CON). Error bars depict 95% Confidence Intervals. Non-overlapping error bars indicate significant group differences. Asterisks indicate significant group differences at the p < 0.05 level of significance.



There were no significant differences between diet group in cumulative distance traveled as measured by running wheel revolutions, although mean distance traveled was slightly higher in rats on a REF diet (Figure 7, left panel).

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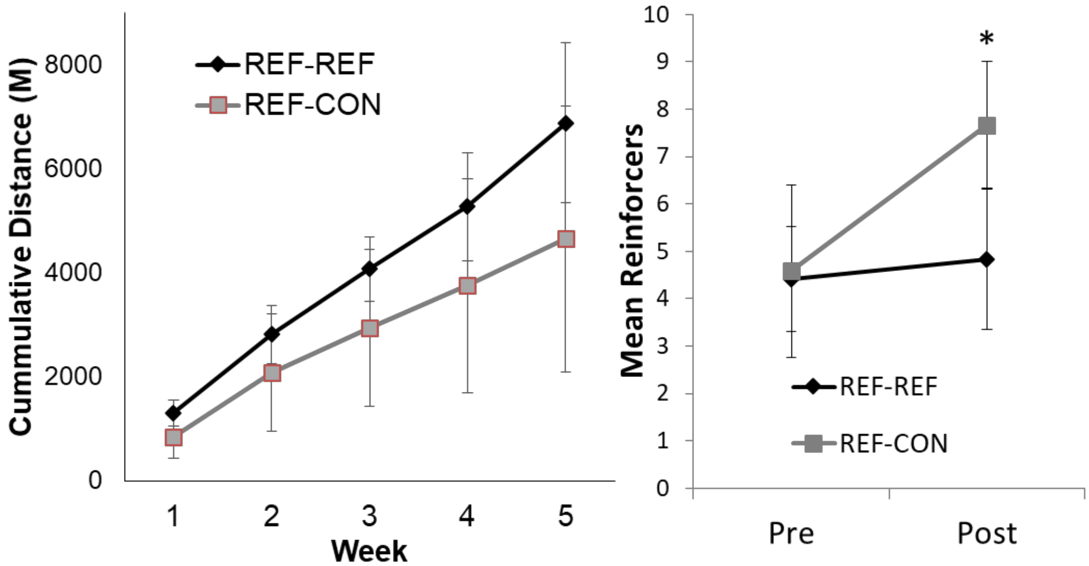
We also assessed changes in motivation using the progressive ratio 5 (PR5) procedure of Blaisdell et al. (2014) [3]. Prior to being placed in the running wheel cages, and while all 8 rats were consuming a REF diet on a restricted feed schedule as implemented in Blaisdell et al., rats received one session of operant lever pressing in which they had to make an increasingly greater number of lever presses to earn each subsequent sucrose reward. As reported in Blaisdell et al. (2014), REF rats showed a low level of responding (Figure 7, right panel, PRE) as we previously reported for rats consuming a REF diet, which was significantly below the breaking points observed in rats fed a CON diet (see Blaisdell et al., 2014). We conducted the PR5 task again after 5 weeks in the running wheel cages, during which time half of the rats had been switched to the CON diet. All rats were food restricted as previously prior to and during the behavioral test. Motivation increased significantly following 5 weeks of consuming the CON diet (Figure 7, right panel, POST), as was supported by a Diet x Time (Pre and Post) Interaction, $F(1, 6) = 6.32$, $p < 0.05$. Planned comparisons revealed a significant increase in reinforcers earned at Post versus Pre diet shift in the REF-CON group, $F(1, 6) = 16.90$, $p < 0.01$, and a difference between diet groups at Post, $F(1, 6) = 7.81$, $p < 0.05$. The number of reinforcers earned by rats switched to a CON diet for 5 weeks was comparable to that shown by rats that only ate the CON diet in Blaisdell et al. Thus, impairments in motivation due to chronic consumption of a REF diet could be reversed with 5 weeks on the CON diet. An alternative possibility is that, despite food restriction, the REF rats were more sated than the CON rats given the higher energy density of the REF diet. We feel this is not as plausible an interpretation since Blaisdell et al. reported that water restricted rats on a REF diet also earned fewer water rewards on a PR schedule than did water restricted rats on a CON diet, suggesting a general motivational impairment induced by the diet rather than differences in food satiety while on food restriction. This extends the previous finding that 9 days of access to a CON diet was not sufficient to improve willingness to work for a sugar reward [3] with a new finding that 5 weeks is sufficient. This may have implications for treatment of diet-induced motivational impairments in humans.

Figure 7. Mean cumulative distance (left panel) travelled across the 5-weeks in the running-wheel cages by rats switched to the CON diet (Group REF-CON) and rats that continued to consume the REF diet (Group REF-REF). Right panel shows mean reinforcers earned in a session where they could lever press to earn a sucrose reinforcer, for rats prior to being placed in the running wheel cages (and thus, all rats were consuming a REF diet), and 5 weeks after being placed in the running wheel cages (and thus, after being switched to the CON diet or remaining

on the REF diet). Error bars denote 95% Confidence Intervals. Asterisks indicate significant group differences at the p < 0.05 level of significance.



General Discussion.

Consuming a REF diet led to greater weight (and adiposity [4]) gain compared to consuming a CON diet, during the first 9 days on the diet (Figure 3). The REF diet has a lot of sugar and is quite sweet. The CON diet is not sweet. This may explain the weight loss in the rats on the CON diet when the sucrose reward was discontinued following the behavioral study (Figure 4, cf [5][6][7]). Once placed back on ad lib feeding, rats on the CON diet regained their lost weight (Figure 4, right panel) by consuming more food (Figure 5). REF diet rats, however, maintained a consistent level of food consumption and stable weight during the same interval, consistent with other studies where rats have constant access to sugar [7].

When rats that had consumed a REF diet over a 9-month period were placed in running wheels, they continued to increase in weight while steadily consuming less food (Figure 6). Rats switched to a CON diet, however, ate less though they only marginally lost weight. But rats that remained on a REF diet did not run less than rats switched to a CON diet. Thus, while switching to a CON diet did improve motivation to work for food (Figure 7), it did not increase activity. What can explain the finding that, when placed in the running wheel cages, rats consuming an obesogenic REF diet ate less than before, ran the same amount as did rats that had been switched to the CON diet, but continued to gain weight? One possible explanation is that rats that remained on the REF diet showed increased reward sensitivity, and the greater activity reflected a motivation to seek more sucrose [8]. Two arguments against this, however, are that a) rats on a REF diet had continuous access to a high-sugar diet, and b) rats showed a reduced, not enhanced, motivation to work to obtain sucrose solution on the PR5 task. An alternative explanation for this paradox could be that rats on the REF diet were suffering from micronutrient deficiencies. In the wild, nutrient poor environments motivate increased time and distance spent searching for food [9]. In the running wheel cages, this increased search motivation would translate to an increased level of wheel running as compared to rats on the CON diet which were nutrient replete. At the same time, the REF diet continued to impair fat metabolism, biasing the endocrine system in favor of fat storage and against lipolysis, possibly due to leptin resistance [10]. This situation might accurately model an all-too-prevalent situation among human dieters of gaining weight while reducing calories and increasing exercise, especially endurance exercise such as jogging or spinning [11]. It is likely the case that this situation occurs primarily when highly processed “junk foods” constitute a significant portion of the diet. Thus, our rat model might be a good animal model to study the paradox of why “you can’t exercise your way out of a bad diet”. Further research is necessary to investigate this hypothesis. If it receives support under further empirical scrutiny, this may be an important approach to understanding weight gain and loss in humans with high translational significance.

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DOI: 10.15310/2334-3591.1084