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The Interaction of Obesity Related Genotypes, Phenotypes, and Economics: An Experimental Economics Approach with Mice

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Abstract

Food intake is greatly influenced by economic factors. Consequently, neuroeconomics has been identified as a new and important area for understanding the interaction between genotypes and phenotypes related to food intake. A foundational element of economics is choice between alternatives. Changing food choices are a central element in the explanation of the increasing obesity rates in human populations. The purpose of this research is to incorporate the key element of choice into the investigation of food intake and weight-related phenotypes for mice in an operant chamber setting. Using normal mice, and mice with a mutation in the Tubby gene (Tub-Mut) which results in adult onset obesity, this research will investigate different behavioral responses among genotypes, as well as unexplored phenotype outcomes when mice are confronted with a falling price of a high fat food relative to a low fat food. Results for both genotypes indicate that as the price of the high fat food falls, consumption of that food increases, but consumption of the low fat food does not decrease in a compensatory fashion. For both genotypes, weight and body fat percentage increases with decreasing high fat food price, but ghrelin and leptin levels do not significantly change. The Tub-Mut shows a significant increase in the area under the glucose tolerance curve, suggestive of a diabetic state. These results show that accounting for choice in neuroeconomic studies is important to understanding the complex regulation of body weight and diabetes.

1. Introduction

There is no debate that genetics and the environment interact in determining health outcomes in individuals and yet we know very little about this interaction. Biological sciences have tended to study genetic factors in isolation from environmental factors. Behavioral sciences, such as economics, have tended to study the environment in isolation from genetics. Indeed, in health economics, one could argue that all of the analysis of economic factors affecting health is done within the ‘black box’ of reduced form analysis because we do not know the biological mechanisms through which these effects occur. For example, the literature is replete with analyses looking at the relationship between income, prices, and health indicators (mortality, disease frequency) but we currently do not remotely understand how these economic factors affect specific biological outcomes determining diseases (e.g., cortisol levels, cholesterol levels, blood pressure). As Deaton [1] (2002 *Health Affairs*) states, “Policy cannot be intelligently conducted without an understanding of mechanisms; correlations are not enough.”

Two of the main problems in understanding the economic-biological mechanism connection in humans are the lack of sufficient data connecting economics and biology and, more importantly, the insufficient control of confounding factors in observational human studies that can distort causal inferences [1]. The nascent interdisciplinary field of neuroeconomics, that integrates behavioral and biological analyses into a single overarching framework, is starting to confront these issues, often employing operant chamber animal models. Operant chamber animal models are appealing because confounding factors can be controlled through experimental design and detailed biological data can be generated in response to changes in the economic environment (e.g., at the organ level, tissue level, and even cellular level) in a relatively short

time. Given the biological sciences have for centuries studied animals to draw inferences about humans, the initial main concern may be the proximity of the economic behaviors of animals with humans. For basic economic principles, this is no concern. There is a substantial economic literature, being published in some of the most prestigious economic journals, on the transcendence of basic economic principles to other species (e.g. [2]).

The purpose of this research is to ask if food choice and genotype affect body weight-related phenotypes in a food cost choice setting. The specific experiment reported here is motivated by the common argument that the increased consumption of high energy-dense food relative to low energy-dense food has been a major contributor to the current obesity epidemic [3-5]. Although there are numerous environmental factors affecting food consumption, economic factors appear especially important [4, 6-9]. As stated by Vaughan and Rowland [10], “There is a pressing need to understand at a fundamental level the interactions between genes and economic change in the environment”, and, “economic decision-making is central to understanding how much and when organisms eat” [11]. The nascent field of neuroeconomics seeks to unravel the relationship between economic decision making, genotypes, and resulting phenotypes and will offer novel insights connecting behavioral and biological sciences [11].

A key determinant in economic decisions is the cost, or price, of obtaining a good. As the price of the good increases the quantity of the good consumed decreases; this is known as the simple law of demand. Through novel experiments, several authors have demonstrated that mice and other species follow this simple law of demand and that food intake will decrease as price increases [10-14].

The simple law of demand is a special case of the more general law of demand that is based on the cornerstone of economics: choice between alternatives [15]. Accounting for choice is

especially important for phenotypes related to food intake and obesity, because different foods have different nutritional characteristics, which in turn can affect obesity-related phenotypes in different ways. For example, if two foods are considered substitutes, as the price of one increases, consumption of that food will decrease, but consumption of the other food will increase in a compensatory or substitution fashion. Consequently, the weight of the animal could decrease or increase depending on the relative consumption of the two foods and their nutritional characteristics. Alternatively, if two foods are considered complements, as the price of one food increases, the consumption of both foods will decrease and weight will decrease. Finally, if two foods are considered independent, then the consumption of one food is not affected by the price of the other. This does not imply weight will necessarily decrease if the price of a food is increased. Consumption of the other food will not change and it may be consumption of this other food that is contributing more to weight. The general law of demand accounts not only for changes in consumption of the good whose price changed (called the own price effect), but also how that change in price may have cross-over effects on the consumption of other goods via choice (called the cross-price effect). Of course, similar to a single food case, in a two-food setting there also may be differences between genotypes in behavioral responses that may lead to differences in phenotypes.

This research therefore extends the current literature regarding mouse neuroeconomic genotypes and food intake to ask if food choice and genotype affect body weight-related phenotypes in a food cost choice setting. In addition to reporting on food intake (low fat, high fat, total) and body weight, we also consider several phenotypes that have not been examined in previous food cost studies: percentage of body fat, serum ghrelin levels, serum leptin levels, and glucose tolerance. While earlier studies have considered economic choice experiments for other

species [2], this protocol has not been applied to mice. Similar to the studies of Vaughan and Rowland [10] who use mice in single food economic studies, there is interest in whether this protocol is applicable to mice as they are the most prevalent model for genetic research related to food intake and body weight. We chose to investigate differences between mice with a mutation in the Tubby gene (Tub-Mut) and normal mice, both of which are genotypes that have not been compared in the literature of operant behavior and food intake. This mutant mouse model displays adult-onset obesity with a phenotype of slight hypophagia and reduced overall physical activity levels in an *ad lib* food setting, suggestive of a defect in behavioral motivation for food or exercise [16]. Thus, the study will examine the effect of choice on body weight parameters, as well as the effect of genotype in a mouse obesity model shown to have reduced behavioral motivation for activities requiring work.

2. Materials and Methods

2.1 *Animals and Environment*

Six Tub Mutant (MUT) (Tub-Mutant C57BL/6) and four Wildtype (WT) (C57BL/6) female mice were obtained from colonies maintained at Virginia Polytechnic Institute and State University, from breeding pairs obtained through The Jackson Labs (Bar Harbor, ME). Mice were genotyped using published procedures [17]. At 6-8 weeks of age all mice were moved to individual shoebox cages with access to water and two jars of 20 mg pellets *ad lib*. One jar contained a low-fat (LF) diet based on the AIN-93g formulation with 16.7% fat, 19.1% protein, and 64.2% carbohydrates [18]. The other jar contained a modified high-fat (HF) diet (35.2% fat, 19% protein, and 45.8% carbohydrates). The diets were formulated to be isocaloric to control for the potential confounding effects of different calorie levels and were supplied by Bio-Serv. (Frenchtown, NJ).

Mice remained in the shoebox cages until they had adapted to the new food, which usually took 2-5 days. After a 12 hr fast, mice were then moved to individual operant chambers measuring 18 x 20 x 14 cm with a steel rod floor. Two levers protruded on one wall of the operant chamber and, internal to the levers, two recessed food troughs. Small cue lights above each lever and each trough indicated operational status (see below). Ad lib water was available from a spout centrally located on the wall opposite the levers. Each operant chamber was housed within a sound attenuated cubicle (77 x 50 x 49 cm) containing a ventilation fan and house light. Operant chambers and housing cubicles, along with computer software, were made by LaFayette Instrument Company (Lafayette, IN). The animals were supplied with a Shepherd Shack (Shepherd Specialty Papers, Milford, NJ) and a neslet (Ancare, Bellmore, NY). Mice remained in the operant chamber through the entirety of the experiments, with the exception of 30 minutes at the end of each day when they were removed for cage cleaning and phenotypic measurements.

2.2 Shaping and Food Procurement Schedule

An argument for the increase in obesity in humans is that high fat foods have become cheaper relative to low fat foods [6-8, 19-21]. The goal of this experiment was to mimic this change and determine how the mice would respond as the price of high fat food decreased relative to the price of low fat food. Consequently, mice first had to be acclimated to a high price level, which for this study is 40 lever presses per pellet, also known as a consumatory fixed ratio (CFR). Food levers and dispensers were operational from 5:00 PM until 9:00 AM everyday for a 16:8 hr feeding/non-feeding cycle. During the feeding cycle, a purchase transaction proceeded as follows. To begin, a cue light above each lever was on. Once the mouse engaged the lever for the chosen food, the cue light of the other food turned off and the lever for that food became inactive. Once the mouse completed all the lever presses required to dispense a pellet for the

chosen food, the cue light over the lever would turn off, the cue light over the associated trough would turn on for two seconds, and the the pellet would be delivered. This would complete the transaction and the system would reset with both lever cue lights turned back on, and the trough lights turned off. Over a four week period, mice were progressed through equal CFR schedules with equal cue light intensity until they reached a CFR of 40 lever presses per pellet for both the low and high fat diets. Every time the prices were changed, the foods were rotated to discourage lever bias (2). The weight and consumption of each mouse was monitored daily to ensure they were eating and maintaining weight.

Once the mice reached the starting prices of 40-40, they were then progressed through the following CFR schedules for the low fat and high fat foods, respectively: 40-40, 40-30, 40-20, and 40-10 presses per pellet. Schedules were in place for 7-10 days and foods were rotated weekly when prices changed. To help reduce learning time, the cue light for low fat high-priced food was set at a slightly lower illumination intensity than the high fat low-priced food. Software from Lafayette Instruments controlled the operant chambers and recorded the number of presses and pellets released.

2.3 Outcome Procedures and Measures

In addition to daily intake and weight measures, body fat percentage was measured weekly with a whole body magnetic resonant imaging (MRI) using a Bruker LF90 NMR analyzer (Bruker Corporation, Billrica, MA). The MRI was conducted on the last day of each schedule (for the starting schedule it was conducted the day before the starting schedule began). A glucose tolerance test (GTT) was conducted on each mouse at the beginning of the 40-40 CFR schedule and again at the end of the final 40-10 CFR schedule. Prior to the test, mice were food deprived

for 12 hours. Tail blood was taken for the fasted measurement and glucose (2g/kg in sterile PBS) was injected intraperitoneally (IP). Tail blood was obtained at 15, 30, 60, 90 and 120 minutes following the injection. Glucose in tail blood was measured using a glucometer (One-Touch Basic, Lifescan, Milpitas CA). At the beginning of the 40-40 CFR schedule, at the end of the final 40-10 CFR schedule, and one day prior to the day of the GTT, blood samples were collected via the cheek pouch bleeding procedure [22]. Blood samples were processed to obtain leptin and ghrelin levels using commercially available kits (Alpha Diagnostics Mouse Leptin Elisa, San Antonio, TX; Millipore Mouse Total Ghrelin Elisa Kit, Billerica, MA). Vaginal smears were taken daily for estrous cycle determination with no significant differences with respect to stage of cycle and other measures noted (data not shown).

2.3 Data Analysis

For data analysis, measures were either daily (food intake and body weight), weekly (body fat percentage), or beginning and ending (ghrelin, leptin, and GTT) for each mouse. Because intake and weight were measured daily, we used the mean values over the last four days of each schedule. Body fat percentage, ghrelin and leptin levels, and GTT were used as measured. Parameters are estimated using repeated measurement two way and one way ANOVAs and post hoc Tukey honestly significant difference (HSD) tests.

3. Results

3.1 Effect on food intake

The effects of changing price on the quantity of high fat, low fat, and total pellets consumed are shown in Fig. 1. The change in price of high fat diet on high fat consumption (the own price

effect) had a negative effect [$F(3,24) = 5.86, P < .01$], and there was no significant main or interaction effects of genotype (Fig 1A). From the initial price of 40 to the final price of 10, mean consumption of the high fat diet across genotypes more than doubled from 46 pellets per day to 110, which was statistically significant at $P < .05$. The complete post hoc Tukey HSD tests indicated that $10 > 30$, $10 > 40$, and $20 > 40$ were significant ($P_s < .05$), but adjacent pairs were not different, indicating that the change in food intake was gradual. A closer genotype consideration by one way ANOVA revealed a highly significant own price effect for MUT mice [$F(3,15) = 6.42, P < .01$] and the post hoc Tukey HSD tests indicated that $10 > 30$, $10 > 40$, and $20 > 30$ ($P_s < .05$). One-way ANOVA for WT indicated no significant price effect on high fat consumption. Thus, MUT animals ate significantly more high fat food overall compared to WT animals.

The effect of the change in price of high fat diet on low fat consumption (the cross price effect) was not significant (Fig 1B). There was also no significant main genotype or interaction effect with genotype. One-way ANOVA by genotype revealed that price effect was significant for the MUT mice [$F(3,15) = 3.29, P < .05$] but this was mainly due to a single statistically significant decrease of low fat food consumption of 47 grams between the 30 and 10 price setting ($P < .05$). For the WT mice, there was no significant cross price effect. Because weight is affected by total caloric intake (not just high fat or low fat), Fig 1C shows the effects of the changing price on the quantity of total pellets consumed. Similar to the own price effect, the effect of the change in price of high fat diet on total consumption was negative [$F(3,24) = 7.64, P < .01$], but there was no significant main or interaction effects of genotype (Fig 1C). The significant differences were that $10 > 40$, $20 > 40$ ($P < .05$) and $10 > 30$ ($P < .06$). One way ANOVA revealed a highly significant price effect on total intake for the MUT mice [$F(3,15) =$

7.42, $P < .01$], but an insignificant price effect on total intake for the WT mice. Thus, MUT mice showed an overall higher total consumption compared to WT mice over the course of the study. This higher total consumption was due to the higher consumption of the lower priced high fat food and no significant change in the consumption of low fat food.

3.2 Effects on body weight and body fat percentages

The effect of the changing price on weight is shown in Fig. 2A. As the price of the high fat diet decreased, weight increased [$F(3,24) = 12.45$, $P < .01$] and results were similar between genotypes, as there was no significant main or interaction effects of genotype (Fig 2A). The post hoc Tukey HSD tests indicated that $10 > 20 > 30$ and $10 > 40$ ($P_s < .05$). One-way ANOVA indicated that the price change effect on body weight was significant for both the MUT and WT ($P_s < .01$). Thus, regardless of genotype, these data suggest an overall weight gain as the price of high fat food is decreased.

There are more differences across genotype in terms of the change in body fat percentage (Fig 2B). The price change effect on body fat percentage was negative [$F(3,24) = 4.78$, $P < .01$] and there was a significant genotype effect [$F(3,24) = 20.50$, $P < .01$] and to a lesser extent a significant interaction effect [$F(3,24) = 2.42$, $P < .10$]. One way ANOVA analysis by genotype showed that the price effects were significant for the MUT [$F(3,15) = 9.32$, $P < .01$], with the Tukey HSD being $10 > 30$, $10 > 40$ ($P < .05$), and $10 > 20$ ($P < .10$). Alternatively, for the WT mice there were no significant differences in body fat percentage related to price. Results therefore indicate that body fat levels in MUT animals were responsive to price, with MUT having higher body fat percentages.

3.3 Effects on ghrelin and leptin levels

Figure 3 shows the relationship between price and the ghrelin levels (Fig 3A) and leptin levels (Fig 3B). Together the results clearly show that mean ghrelin and leptin levels increased between the high price level of 40 and the low price of 10. There was, however, a great deal of variability around these means and there were no significant price, genotype, or price-genotype interaction effects between price and ghrelin levels or leptin levels.

3.4 Effects on glucose tolerance test

Figure 4 shows the relationship between price and glucose tolerance test results for both genotypes. The average blood glucose curves for each genotype given a glucose tolerance test after the high and low price schedules are shown in Fig. 4A (WT) and Fig 4B (MUT). In MUT animals, blood glucose levels declined more slowly following low priced high fat food price schedule. In WT there was no effect on the curve at either price schedule. This is shown more clearly in Fig. 4C, which displays the area under the curve (AUC) for both genotypes at each price schedule. The price change effect on AUC was negative [$F(1,8) = 5.70, P < .05$] and there was a significant genotype effect [$F(1,8) = 10.31, P < .05$] with a less significant price-genotype interaction effect [$F(1,8) = 4.28, P < .10$]. As shown in Fig 4C, these significant price effects were associated with the MUT mice [$F(1,5) = 10.82, P < .05$], as there was no significant price effect for the WT mice. Results suggest there is an improvement in glucose tolerance when prices of high fat food are high. However, neither genotype showed an overt glucose intolerance phenotype with low-priced high fat food.

4. Discussion

This study shows that a choice-based operant chamber protocol can be applied to mice with general results comparable to other species. As in studies using other species and consistent with economic theory [13, 17, 23-25], mice respond to economic incentives in a choice environment. For MUT and WT mice together, as the price of the high fat food decreased relative to the low fat (isocaloric) food, the average consumption of high fat food significantly increased following the law of demand, which is consistent with numerous single food foraging studies [10-14]. Somewhat more surprising is that the average consumption of the low fat food did not change, indicating there was no significant cross-price effect and no compensatory decrease in the consumption on average. In economic parlance, the foods are classified as independent, so it is not just the increase in high fat food that is contributing to weight gain and the other phenotype changes, but also the lack of a compensatory decrease in the consumption of the low fat (isocaloric) food. Nothing from economic theory rules out this possibility as the degree of substitution will depend on numerous factors, such as the context, quality similarities, purpose similarities [24], and even the type of substitution being measured (e.g., net versus gross [15]). Taken together, the total food intake (high + low fat) increased as the price of high fat food decreased. Importantly, the MUT mice did show greater responses in high fat, low fat, and total intake to the price change than did the WT mice, but these response differences were not statistically significant. These results are in contrast to those obtained by Coyle, Strand, and Good [16] with WT and Tub-Mut mice of a similar age and over a similar time frame (5-20 weeks) but in an *ad lib* feeding environment with a single food. Specifically, Coyle, Strand, and Good [16] report a daily mean consumption for WT of ~4.30 g/day but for MUT ~4.0 g/day ($P <$

0.01), indicating MUT mice ate *less* than WT in their ad lib setting. Alternatively, in our operant chamber economic setting, daily mean total intake for each genotype was about half of the expected ad lib intake, and there were no significant differences between TUB-MUT and WT. Specifically, at 20 mg per pellet, our daily mean total consumption over the length of this study was ~2.16 g/day for MUT and ~1.92g/day for WT and these amounts were not statistically different. Some of these discrepancies may be attributable to differences in kcals/gram. Our pellets had 3.77kcals/gram, whereas the standard chow fed by Coyle, Strand, and Good [16] had 3.02 kcals/gram, but these differences do not contribute to the reversal in relative consumption between genotypes. Thus, in our non ad libitum environment, hypophagia for the MUT mice disappears, and there is an overall slight but non-significant increase in intake (0.95 kcal/day) for the MUT mice relative to WT mice.

With respect to weight in a single food setting, the relationship between food price and weight is expected to mimic the simple law of demand: as the price goes up (down) intake and weight would therefore decrease (increase). In various settings, this result has been confirmed [14, 26], although not universally [10]. However, once the important environmental attribute of choice is allowed, the weight-price relationship is no longer clear even *a priori* because weight will depend on total intake, which depends on consumption of both foods; that is the degree of substitution and own and cross-price effects. In our experiments, we found that as the price of high fat food decreased, total intake and weight increased for both TUB-MUT and WT, but there were no significant differences between TUB-MUT and WT. This is in contrast to the results of Coyle, Strand, and Good [16], where the TUB-MUT weighed significantly more compared to the WT over the course of their study on *ad lib* feeding. Of note, those studies used male mice, which generally weigh more than females. Females, on the other hand, generally have more body

fat, and our results in this area (discussed below) do indicate a genotype difference. Overall, the weight response differences between TUB-MUT and WT in the *ad lib* setting versus a choice cost setting underscore the importance of the economic environment and the role choices can play in body weight related phenotypes.

Although we did not find any differences in weight between the TUB-MUT and WT, there were significant differences in body fat percentage. The TUB-MUT responded significantly to the change in price and therefore showed a substantially higher body fat percentage. This outcome is consistent with the carcass fat content analysis performed by Coyle, Strand, and Good in their *ad lib* setting [16].

The increasing body weight and body fat percentage, especially for the TUB-MUT, was not accompanied by any change in leptin or ghrelin levels, though there was a significant increase in the area under the glucose tolerance test curve for the TUB-MUT. As indicated in the introduction, we are not aware of other foraging/cost experiments that have looked at leptin, ghrelin, or glucose tolerance, but the diet-induced obesity literature has documented changes in all three of these phenotypes in *ad lib* settings [27, 28], again underscoring the need for more research on the interaction of economics, genotype responses, and phenotype outcomes.

This research has answered calls for more analysis on behavioral economics and genetics by incorporating a key feature of economic decision-making: choice. Food choice is especially important for biological outcomes, as the outcomes may depend more on the composition of foods consumed rather than the actual intake of a single food. In addition, most choice/substitute research has focused on behavioral issues and effects rather than biological outcomes. Moving to studying the biological effects of economic factors is an important research area because many

government policies designed to fight obesity are economic policies, such as taxes on certain foods [29, 30], and these policies not only have direct effects but can also have indirect effects via their influence on the choices of alternative foods. The complete efficacy and effectiveness of these policies in improving health cannot be fully appreciated until we understand not only the behavioral but the biological influences of choice on obesity. In addition, neuroeconomic research that incorporates choice will give us a better understanding of how choices are actually made and the factors that affect choices.

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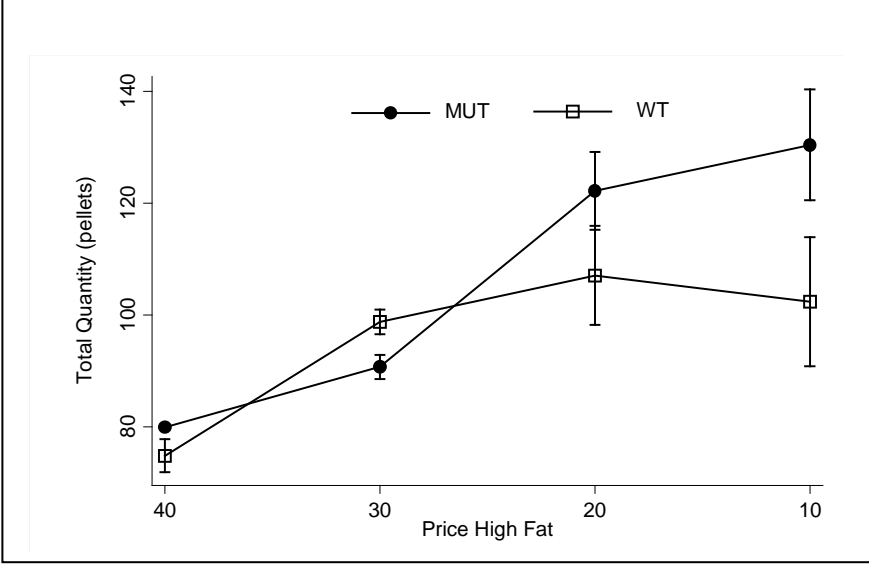
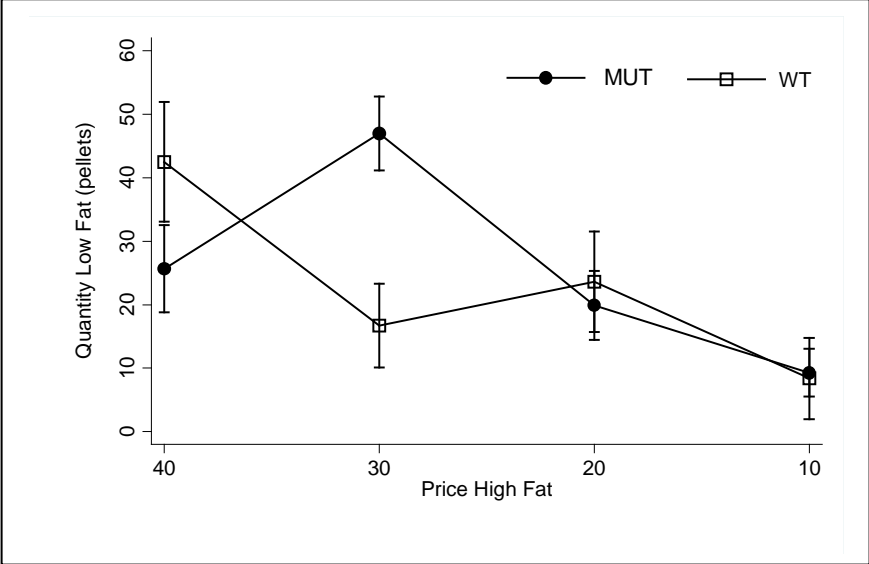
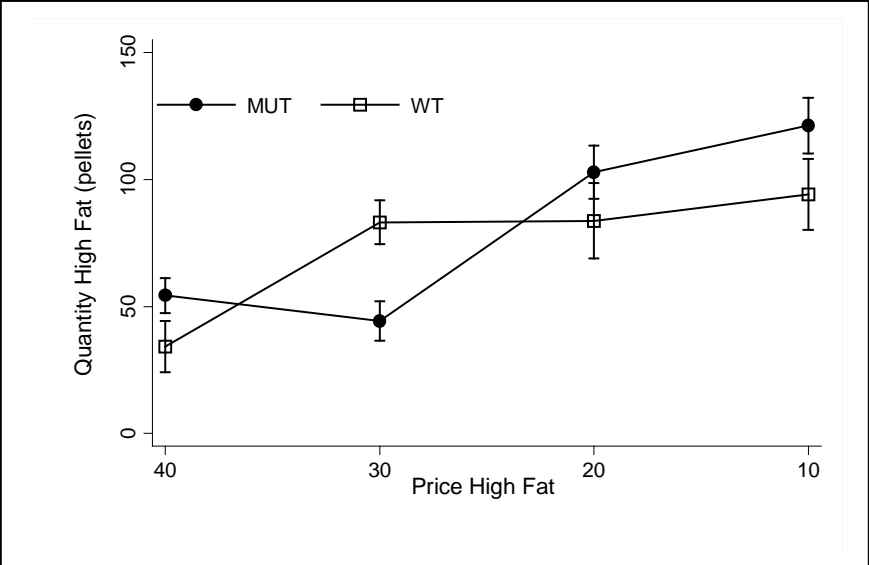
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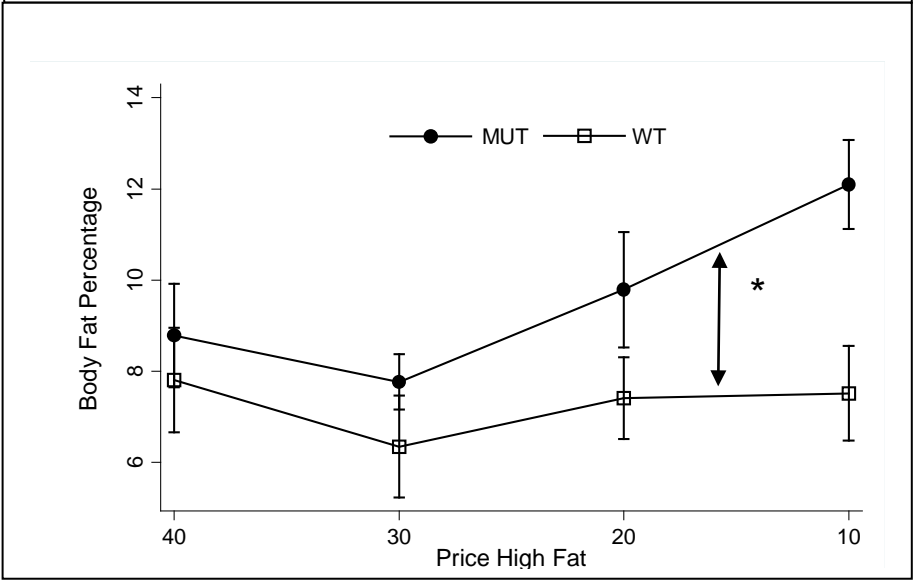
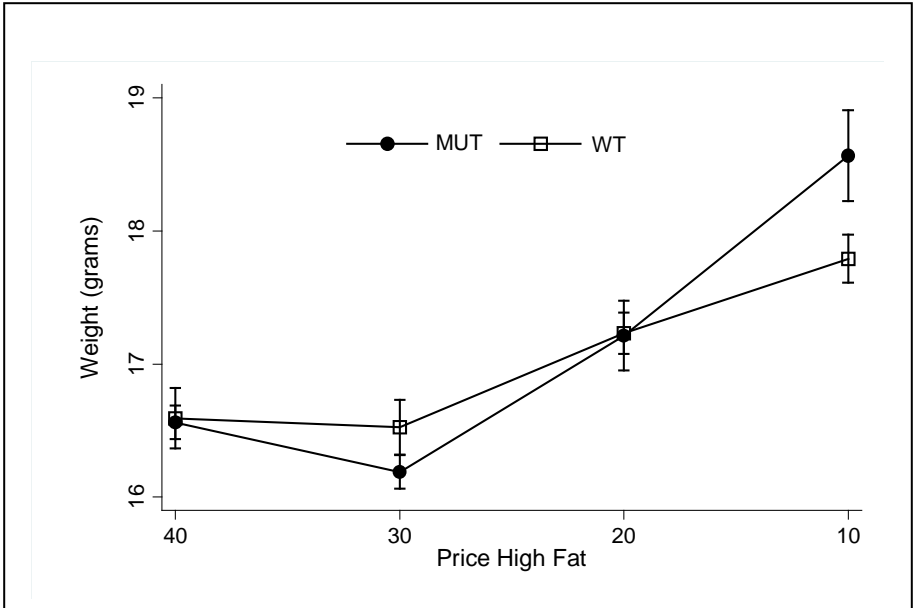
Figure 1. Food consumption group means \pm S.E. (A) high fat consumption, (B) low fat consumption, and (C) total consumption versus price change by genotype.

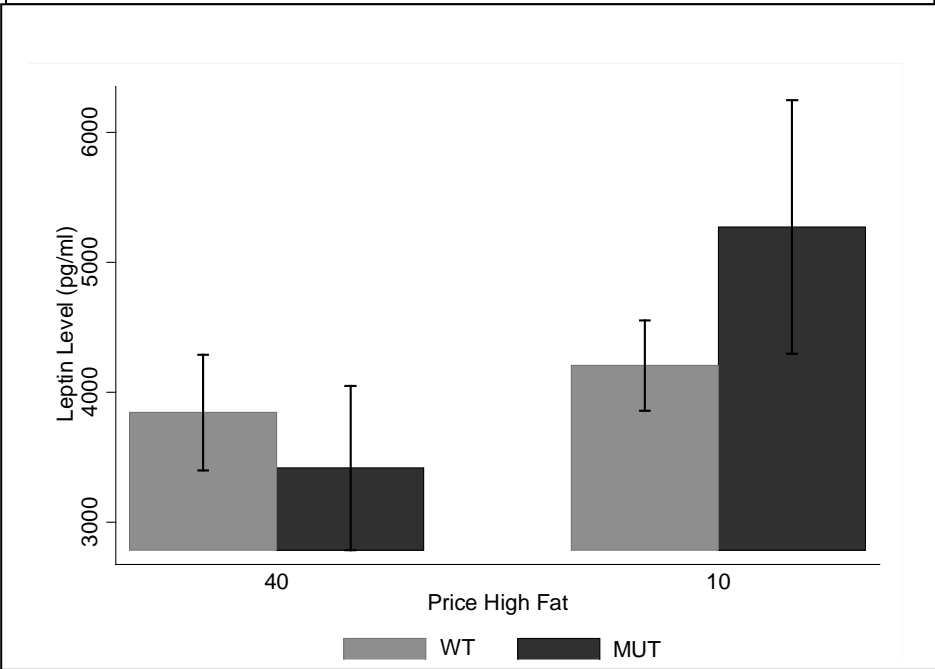
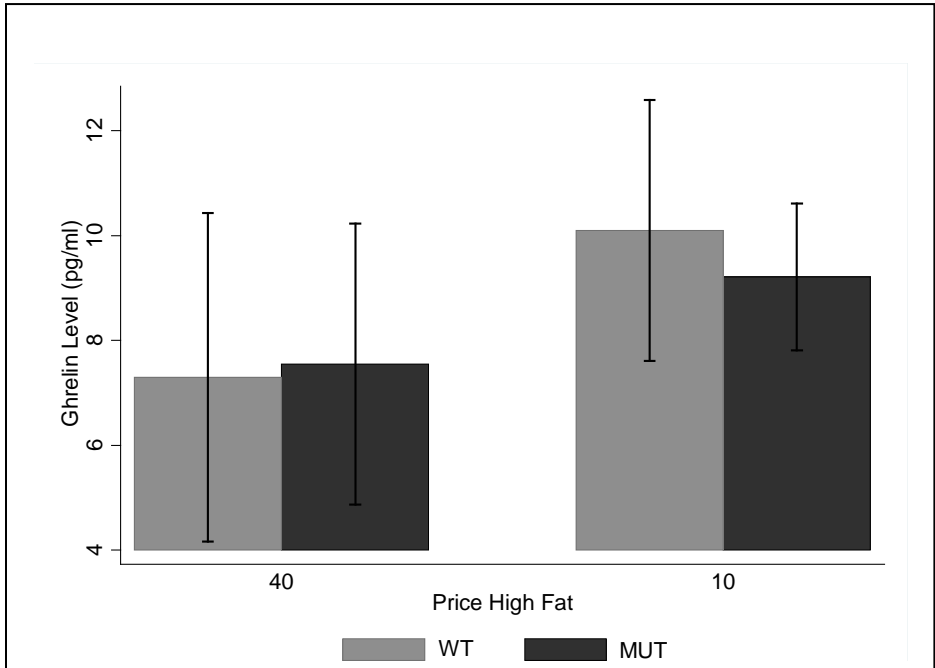
Figure 2. Body weight (A) and body fat (B) group means \pm S.E. versus price change by genotype. * $P < .05$ MUT vs. WT for the entire schedule.

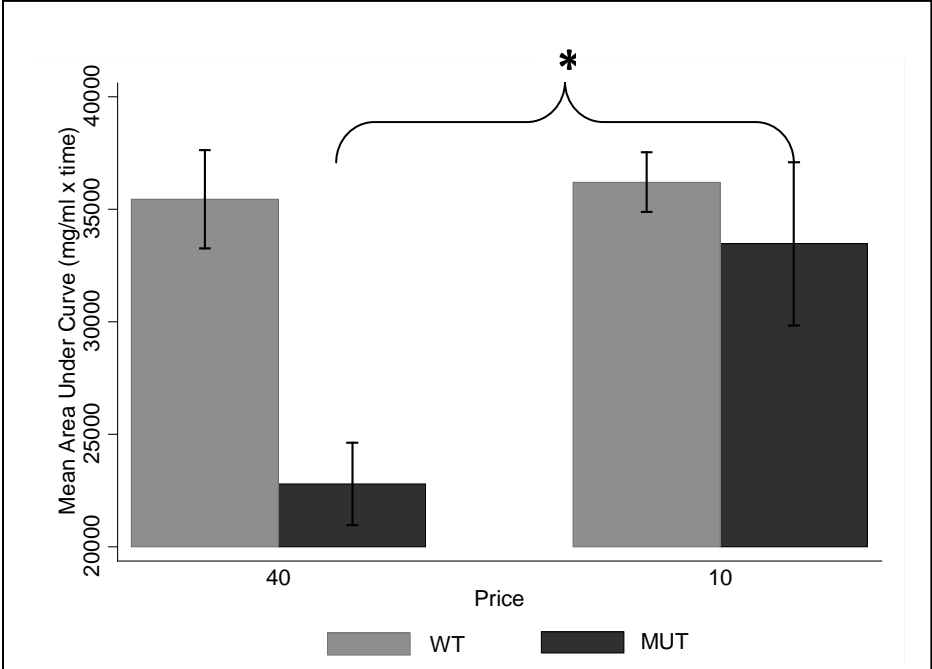
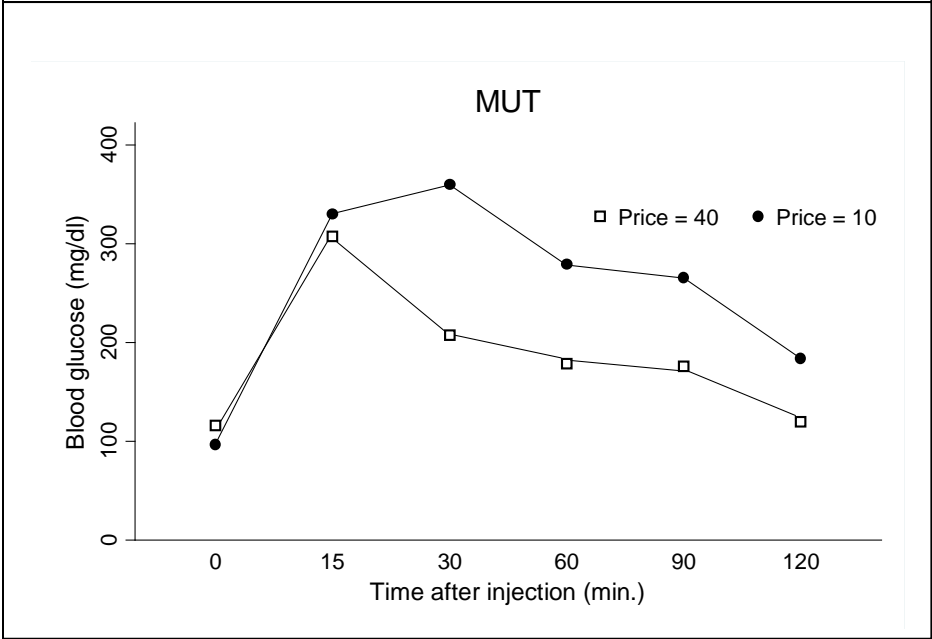
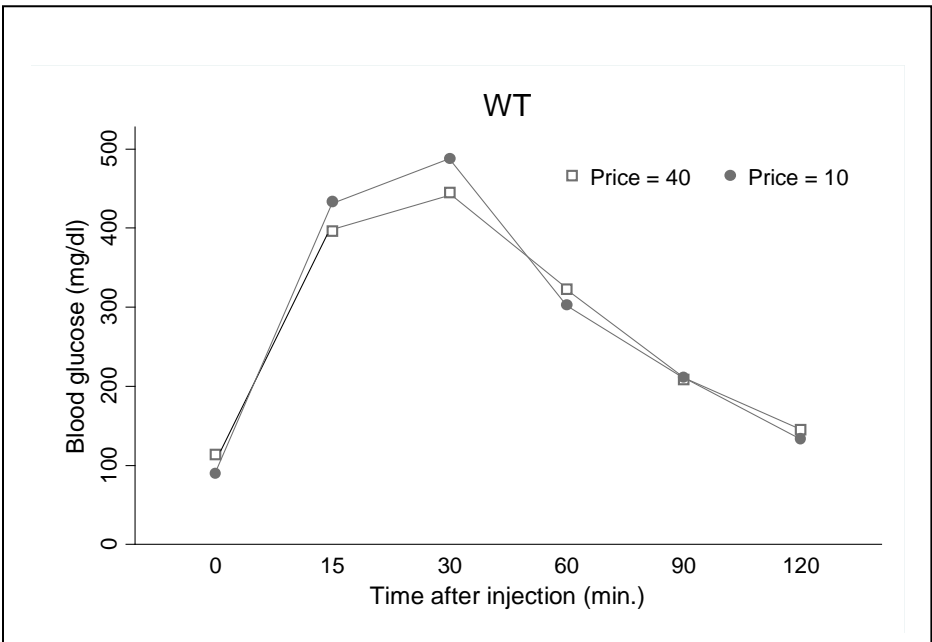
Figure 3. Changes in ghrelin (A) and leptin (B) group mean \pm S.E. versus price change by genotype.

Figure 4. Glucose tolerance tests versus price change by genotype. Group mean blood glucose tolerance test curve versus price for WT (A) and MUT (B) . Group mean \pm S.E. changes in area under glucose tolerance test curve versus price change by genotype (C). * $P < .05$ MUT at 40 vs. MUT at 10.









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