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Unraveling the Obesity of OLETF Rats

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Abstract

Cholecystokinin (CCK) is a brain gut peptide that plays an important role in satiety. CCK inhibits food intake by reducing meal size. CCK's satiety actions are mediating through its interaction with CCK1 receptors. Otsuka Long Evans Tokushima Fatty (OLETF) rats are a CCK1 receptor knockout model that allows the study of multiple CCK functions. OLETF rats are hyperphagic with the hyperphagia expressed as a significant increase in the size of meals. OLETF rat obesity is secondary to the hyperphagia and has been propose to derive from two regulatory deficits. One is secondary to the loss of a feedback satiety signal. The other results from increased dorsomedial hypothalamic NPY expression. Recent studies have examined developmental aspects of altered feeding, body weight and orexigenic signaling on OLETF rats. OLETF rats demonstrate increases in meal size in independent ingestion tests as early as two days of age. OLETF pups are also more efficient in suckling situations. Consistent with such developmental differences, examinations of patterns of hypothalamic gene expression in OLETF pups indicate significant increases in DMH NPY expression as early as postnatal Day 15. Access to a running wheel and the resulting exercise have age dependent effects on OLETF food intake and obesity. With running wheel access shortly after weaning, food intake decreases to the levels of LETO controls. When running wheel access is discontinued, food intake temporarily increases resulting in an intermediate phenotype and the absence of diabetes. Together these data demonstrate roles for peripheral CCK and CCK in feeding and body weight control and support the use of the OLETF rat as a model for examining obesity development and for investigating how interventions at critical developmental time points can alter genetic influences on food intake and body weight.

Introduction

Genetic obesity models have the potential to identify a range of factors that contribute to obesity development. Rodent models were instrumental in the identification of leptin, the adiposity signal that is a major influence on energy balance. Ob/ob mice lacking leptin were first identified in the 1970's but it was not until the mid 1990's that leptin was identified as the missing protein that led to obesity in this model (1). The identification of leptin greatly advanced our understanding of hypothalamic systems involved in energy balance. Leptin's major site of action is the hypothalamic arcuate nucleus where leptin interacts with two distinct neuronal subtypes, one containing the orexigenic peptides neuropeptide Y (NPY and agouti related peptide (AgRP), and the other containing the prepropeptide, proopiomelanocrtin (POMC), that produces the anorexigenic peptide alpha melanocyte stimulating hormone (α-MSH) (2). A variety of obesity models have now been identified that involve defects in aspects

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of the leptin signaling pathway and its downstream mediators (3–6). Other rodent obesity models that do not derive from deficits in the leptin signaling pathway have also been identified. This review will focus on one such model, the OLETF rat and how study of this model and its metabolic and behavioral deficits have identified novel actions of hypothalamic signaling in the controls of food intake and developmental events that contribute to overall energy balance.

OLETF Rats

In response to the appearance of a spontaneous obesity in an outbred colony of Long Evans rats, Otsuka Pharmaceuticals developed two lines of rats by selective breeding. These are now referred to as the obese Otsuka Long Evans Tokushima Fatty (OLETF) and the control Long Evans Tokushima Otsuka (LETO) (7). OLETF rats were initially characterized as having late onset hyperglycemia, polyuria, polydipsia and mild obesity and were studied as a model of non insulin dependent diabetes mellitus (NIDDM – type II diabetes) (7).

OLETF rats are hyperphagic, consuming roughly 30% more than LETO controls. They become obese, with male and female OLETF rats demonstrating different weight trajectories compared to LETO controls. Ten week old male OLETF rats weigh 25–30% more than LETO controls and at this age the difference in female rats is less. With aging, the degree of obesity in male rats peaks at about 35% while it increases beyond that in females (LETO males eventual become obese lessening the difference between OLETF and LETO rats while LETO females do not become obese). The OLETF rat differs from other rat obesity models in that their fat deposition is predominately intra-abdominal or visceral. In other models such as the Zucker rat, fat deposition is predominately subcutaneous (8). OLETF rats have impaired glucose tolerance by 5 weeks of age, a time point at which there is not a reliable increase in body weight compared to LETO controls. With age, the degree of glucose intolerance increases and both male and female OLETF rats become clearly hyperglycemic and hyperinsulinemic. A significant proportion of male OLETF rats eventually develop insulin dependent diabetes (7).

Studies characterizing overall pancreatic function in the OLETF rat initially demonstrated the absence of a pancreatic acinar cell response to the brain/gut peptide cholecystokinin (CCK) (9). This lack of a response to CCK led to investigations of CCK receptor distribution and function in the OLETF rat, resulting in the detection of an absence of CCK-1 receptor gene expression. Southern blot analysis failed to show a restriction band consistent with the CCK-1 receptor gene in OLETF rats and cloning and sequencing of the CCK-1 receptor gene in the OLETF rat identified a 6847 base pair deletion in the gene that spanned the promoter region and the first and second exons (10). This deletion and its accompanying disruption of CCK-1 receptor protein production make the OLETF rat a naturally occurring CCK-1 receptor knockout model.

CCK and CCK-A Receptors in Food Intake Control

CCK is a brain/gut peptide that is released from the proximal intestine in response to the intraluminal presence of nutrient digestive products (11). Endogenously released CCK plays a variety of roles in modulating overall digestive function. It slows gastric emptying, stimulates pancreatic and gall bladder secretion and modulates intestinal motility (12). CCK has also been show to play a role in satiety. Exogenous peripheral administration of CCK reduces food intake and results in the earlier appearance of satiety (13). CCK's actions are specific to meal size. Meal contingent administration of CCK in rats produces consistent reductions in the size of meals without altering total food intake (14). Meal frequency increases to compensate for the decrease in meal size. The actions of exogenous CCK mimic those of the endogenous peptide. Administration of CCK antagonists result in increases in meal size and, in the sort term, increases in food intake (15,16). The feeding inhibitory actions of CCK are peripherally

mediated with major sites of action being the afferent vagus (17) and the circular muscle layer of the pyloric sphincter (18).

CCK's feeding inhibitory actions are mediated through interactions with CCK-A receptors. Two CCK receptor subtypes have been identified. These were originally pharmacologically characterized based on differential affinities of various CCK binding sites for various CCK fragments and analogs (19). Two G protein coupled CCK receptor proteins have now been identified and the genes responsible for their expression have been sequenced (20,21). The distribution of CCK receptors is species specific. In rat, CCK-A (now referred to as CCK-1) receptors are expressed in the pancreas, pyloric sphincter, vagal afferent cell bodies in the nodose ganglion and in a limited number of brain sites (19,22). CCK-B receptors (now referred to as CCK-2 receptors) are found in stomach, intestine, nodose ganglion and are widely distributed throughout the brain (19,22). Work with CCK receptor antagonists with relative specificity for one or the other receptor subtype has demonstrated that the feeding inhibitory actions of both exogenous and endogenous CCK with depends upon of CCK-1 but not CCK-2 receptor interactions (16,23).

Disordered Food Intake in OLETF Rats

OLETF rats lacking CCK-1 receptors are insensitive to the feeding inhibitory actions of exogenous CCK (24). Meal pattern analyses from tests in which rats had 24 hour access to 45 mg food pellets demonstrated specific alterations in meal size in OLETF rats (24). As show in Figure 1, OLETF rats had almost twice the average meal size of LETO controls. In response to this increase in the size of their spontaneous meals, meal frequency decreased but not sufficiently to compensate for the increase in meal size, resulting in a relative overall hyperphagia. Analysis of the microstructure of consuming liquid nutrients reached similar conclusions - increased durations of drinking consistent with impaired satiety without changes in the initial rates of consumption (24). The role of the increased food intake in the obesity of the OLETF rat was evaluated in pair feeding studies in which one group of OLETF rats were fed the amounts consumed by ad lib fed LETO rats. As demonstrated in Figure 2, pair feeding completely prevented the OLETF obesity leading to the conclusion that the obesity is secondary to the increased food intake (25). Importantly, pair feeding also normalized fat pad weight, and plasma glucose and insulin levels in OLETF rats, further highlighting the role of the increased food consumption in the obesity and diabetes of OLETF rats (25).

OLETF rats have also been demonstrated to over consume both dietary fat and sweetened foods. Consistent with a role for peripheral endogenous CCK in mediating the satiating effects of fatty foods, OLETF rats have deficit in satiety for fatty foods. They decrease their food intake less than LETO control rats in response to gastric or intestinal lipid infusions (26). Furthermore, OLETF rats over consume high fat diets to a greater degree than do LETO control rats resulting in an exacerbation of their obesity (26,27). OLETF rats have also been demonstrated to have increased taste preference for sucrose that generalizes to other sweet tastants (28). This preference is expressed both as a function of age and tastant concentration. The preference is due to taste since it occurs with sham feeding (29). Furthermore, OLETF rats demonstrate conditioned preferences to sweet stimuli that are independent of the caloric value of the tastant (30). This reduction in the satiating ability of fats and increased preference for sweet taste both likely contribute to the overall hyperphagia in OLETF rats.

Hypothalamic Signaling in OLETF Rats

The finding of altered meal size is consistent with a deficit in peripheral CCK signaling. However, the lack of compensation and the overall increase in food intake is not. Data from earlier studies using meal contingent CCK administration had demonstrated alterations in meal frequency in response to CCK-induced alterations in meal size (14). This difference in findings

raised the possibility that there were additional contributing factors to overall hyperpahgia in the OLETF rat. Hypothalamic peptide signaling systems have been demonstrated to play important roles in energy balance and their disturbance can lead to obesity. The pair feeding study discussed above that demonstrated that OLETF obesity was secondary to their hyperphagia also allowed an assessment of the potential role of alterations in hypothalamic neuropeptide signaling in the hyperpahgia and obesity of OLETF rats (25). Levels of mRNA expression for the orexigenic peptide NPY and the precursor of anorexigenic peptide MSH (POMC) in the hypothalamic arcuate nucleus were consistent with the rats' food intake. NPY expression was decreased and POMC expression was increased in obese OLETF rats and both of these alterations in gene expression were normalized by pair feeding. In contrast, while there was no evidence of altered NPY mRNA expression in the dorsomedial hypothalamus (DMH) of ad lib fed OLETF rats, the level was greatly elevated in pair fed, weight normalized OLETF rats (Figure 3). Increased DMH NPY in weight normalized OLETF rats raised the possibility that increased expression of this orexigenic signal could be driving their hyperphagia and preventing them from compensating for the increase in meal size. This possibility was supported by data demonstrating increased levels of DMH NPY mRNA expression in preobese 5 week old OLETF rats (25).

Why should the absence of CCK-1 receptor signaling alter DMH NPY mRNA expression? Although the great majority of rat brain CCK receptors are the B subtype, it has long been recognized that there are specific nuclei in which CCK-1 receptors are found. The DMH is one such location. In fact, in the intact rat, CCK-1 receptors and NPY are colocalized in a neuronal population within the compact subregion of the DMH (31). Furthermore, local CCK administration results in a down regulation of NPY expression and a decrease in food intake, suggesting that CCK normally plays a role to modulate DMH NPY and, in the absence of such modulation, NPY expression is increased as is overall food intake. Together, these data have led to the suggestion that the hyperphagia in OLETF rats is the result of two regulatory deficits (32). One, resulting from the absence of vagal CCK-A1receptors and the loss of a within meal satiety signal produces increases in meals size. The other, resulting from the absence of DMH CCK-1 receptors and the loss of an inhibitory influence on DMH NPY expression, prevents the OLETF rat from compensating for the increased meal size. Consistent with this suggestion is the finding that CCK-1 receptor knockout mice have a deficit in meal size but are neither hyperphagic or obese (31). Mice have a different CCK receptor distribution from that of rats and, in the mouse, CCK-1 receptors are not expressed in the DMH. Thus, mice lacking CCK-1 receptors appear to have a single regulatory deficit and are able to compensate for the absence of a peripheral satiety signal (31).

Development of Ingestion in OLETF Rats

Although OLETF rats are not significantly heavier than LETO controls at 5 weeks of age, developmental studies have identified a number of important behavioral differences that presage their later obesity. OLETF dams exhibit more frequent bouts of nursing (33) and OLETF pups consume more milk in individual suckling bouts (34). This is not simply a function of an increased milk supply in the obese OLETF dams. When LETO and OLETF pups are given access to the same dams, OLETF pups consume more whether they are with an OLETF or LETO dam. OLETF pups also consume more sweetened milk in independent ingestion tests than LETO controls as early as postnatal day 2 (35). Consistent with a satiety deficit, this increased intake could be attributed to increases in both meal size and meal duration. Thus, OLETF pups gained more weight than aged matched LETO controls in the ingestion tests and behavioral observations identified that they continued to consume the sweetened milk after the LETO pups had stopped. Young OLETF rats also consumed more rapidly at the beginning of the ingestion test suggesting that increased ingestion was not simply the result of an impairment in satiety. Although not significantly heavier at weaning, OLETF pups are

heavier at earlier time points and have increased fat deposition throughout this period (36). Consistent with these early effects on ingestive behavior in LETO rats, preweanling LETO rats have significant increases in DMH NPY (37).

OLETF Rats' Responses to Exercise

Shima and colleagues (38) originally demonstrated that providing OLETF rats with access to a running wheel resulted in significant decreases in their rate of body weight gain and had a preventive effect on the development of type II diabetes. Further study has demonstrated that the effects of exercise on the development of obesity in the OLETF rat are multiple and depend upon the age of the rats at the time that the opportunity for exercise is provided. In adult OLETF rats access to a running wheel and the subsequent activity result in reductions in body weight down to the level of age matched LETO rats. When access to the running wheel is discontinued, body weight increases and comes right back up to the level of aged matched OLETF rats that did not have running wheel access. Thus, in the adult OLETF exercise can ameliorate their obesity (39) and, as reported by Shima and colleagues (38) normalize blood glucose and insulin levels. However, the effects of exercise in adult OLETF rats are temporary.

Access to a running wheel in young OLETF rats has different short and long term effects. As shown in Figure 4, when running wheel access is provided to OLETF rats at 6 weeks of age, the rate of body weight gain stops and weight remains stable until the OLETF rats reach the weight of aged matched LETO controls. They continue to track the weight of LETO controls for as long as access to the running wheel is continued. In contrast, access to the running wheel and increased activity does not affect the rate of weight gain in LETO rats. They continue to gain weight at the same rate as sedentary LETO controls. When access to the running wheel is discontinued following 8 weeks of exercise in OLETF rats, some weight is regained but OLETF rats with past running wheel access never reaches the weight of aged matched OLETF rats that did not have running wheel access. Thus, there are lasting effects of exercise on the phenotype of OLETF rats (40).

The changes in body weight in OLETF rats are not simply the result of increased energy expenditure. Although OLETF rats engage in more activity overall than LETO controls, running wheel activity also produces significant changes in food intake in the OLETF rats. As shown in Figure 5, food intake of OLETF rats with running wheel access decreases sharply and remains at the same levels of LETO rats with running wheel access. When running wheels are relocked, food intake again increases but does so only temporarily. When weight gain stabilizes, food intake is reduced and OLETF rats no longer demonstrate hyperphagia.

Examinations of patterns of hypothalamic gene expression revealed both short and long term effects of exercise. Following 4 days of running wheel access, both OLETF and LETO rats had significant elevation in DMH corticotrophin releasing factor (CRF) mRNA expression. This change was specific to the DMH as CRF expression in the paraventricular nucleus (PVN) was not elevated by exercise. As shown in Figure 6, DMH CRF expression continued to increase for as long as running wheel access was maintained and returned to baseline levels within 4 days of locking the running wheels. Elevated levels of DMH CRF have been associated with exercise induced anorexia as infusion of a CRF antagonist significantly attenuates the temporary decrease in food intake that takes place with increased exercise in intact rats. Thus, the decrease in food intake in the OLETF rat in response to exercise may be mediated in part by the increase in DMH CRF mRNA expression (40).

Running wheel access also affected DMH NPY mRNA expression (Figure 7). There were no short-term effects on DMH NPY in either LETO or OLETF rats. However, 12 weeks of exercise resulted in elevated DMH NPY in both groups. Importantly, although elevated in weight normalized exercising OLETF rats, the elevations in DMH NPY mRNA expression were not

nearly of the same magnitude reached in pair fed OLETF rats as discussed above. Furthermore, levels of NPY DMH expression were completely normalized in OLETF rats for whom the running wheels were relocked. Thus, exercise appears to exert a control on DMH NPY mRNA expression even in the absence of CCK1 receptor signaling and this lasting control appears to be age dependent (40).

Exercise also has long-term effects on glucose homeostasis in the OLETF rat. Within 4 days of running wheel access, plasma glucose levels are normalized and remain s for the duration of running wheel access. Importantly, even in rats with discontinued running wheel access and with some body weight gain, plasma glucose levels remain normal and are significantly decreased from levels found in aged matched sedentary OLETF rats. Thus, exercise during this developmental stage has lasting effects on glucose homeostasis, preventing OLETF rats from developing type II diabetes (40).

Summary and Conclusions

The OLETF rat provides a novel obesity model in which the genetic defect is independent of the leptin signaling pathway. OLETF rats lacking CCK1 receptors are hyperphagic following weaning and, in response to the increased food intake, become obese. Consistent with a deficit in satiety signaling, food intake in the OLETF rat is characterized by increased meal size. OLETF rats also have a deficit in DMH NPY signaling. In the absence of DMH CCK1 receptors, DMH NPY is greatly overexpressed. We interpret this increase as the basis for the failure to compensate for the peripheral satiety deficit. The identification of a role for the DMH and specifically DMH NPY in the disordered feeding of the OLETF rat, significantly advances our understanding of the role of the DMH in energy balance. Prior studies had demonstrated that DMH lesions result in mild hyperphagia and obesity but the specific cause of the obesity had not been identified (41). Furthermore, other studies had demonstrated increased DMH NPY mRNA expression in a number of states of increased caloric demand, such as lactation (42) or chronic food restriction (43). The results with the OLETF rat now provide a context for such findings and suggest that the major output of the DMH in energy balance is orexigenic and derives from the NPY expressing neurons. Furthermore, CCK acting through CCK-1 receptors inhibits DMH NPY and, in that way, plays an overall inhibitory role on food intake.

Preweanling OLETF rat pups evidence a number of alterations in ingestive behavior. They overconsume in nursing bouts whether from their own or from a LETO control dam. They also over consume in independent ingestion paradigms. These data suggest the presence of a satiety deficit even at early ages. Exogenous CCK has the ability to inhibit independent ingestion in newborn rats as early as postnatal day 1 (44) but the role of endogenous CCK in ingestive control has been thought to emerge later in development (45). The results with OLETF rats demonstrating increased intake expressed as prolonged licking as early as postnatal day 2 suggest an earlier role for endogenous CCK in ingestive control. As in adult OLETF rats, the pattern of behavioral results are not easily accounted for by simply a satiety deficit. OLETF pups ingest with a shortened latency and have higher initial lick rates suggesting a greater avidity/and or preference for the nutrient source. Whether this arises from the absence of DMH CCK-1 receptors or has to do with fundamental differences in taste physiology remains to be determined. Both CCK and CCK-1 receptors are present on taste receptor cells and CCK modulates the excitability of taste receptors (46,47). The absence of such an action may contribute to the increased sweet preferences in adult OLETF rats and to the apparent increased avidity for sweetened fat in neonates.

The effects of exercise on food intake and the development of obesity and type II diabetes in the OLETF rat are age dependent. When young OLETF rats are exposed to a running wheel, there are lasting effects on the expression of the consequences of the absence of CCK1

receptors. OLETF rats with early running wheel experience are less obese, are not hyperphagic and do not develop diabetes. How exercise modifies the phenotype in these ways remains to be determined but the overall phenomena point to how early environmental experiences can shape eventual outcomes. Lasting effects of altered fetal environment on metabolic phenotype are now well documented (48–50). These data with exercise suggest that critical periods for affecting aspects of metabolism may extend to later ages.

Thus, studies in the OLETF rat have identified additional roles for CCK in food intake control, expanded the focus on NPY in appetite control from the hypothalamic arcuate nucleus to include the DMH, and demonstrated effects of exercise that can have lasting effects on energy balance. All of these findings were unexpected and their identification demonstrates the multiple ways in which genetic models can illuminate controls of energy balance.

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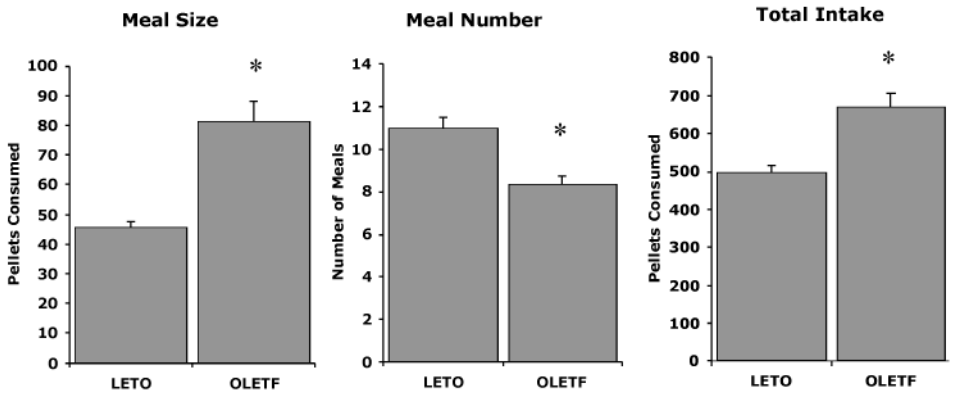

Figure 1.
Meal patterns and total food intake in LETO and OLETF rats. OLETF rats consume significantly larger meals. In response to the increased meals size, meal frequency decreases. However, the decrease in meal size is not sufficient to compensate for the larger meals, resulting in an overall hyperpahgia. * designates significant difference form LETO control.

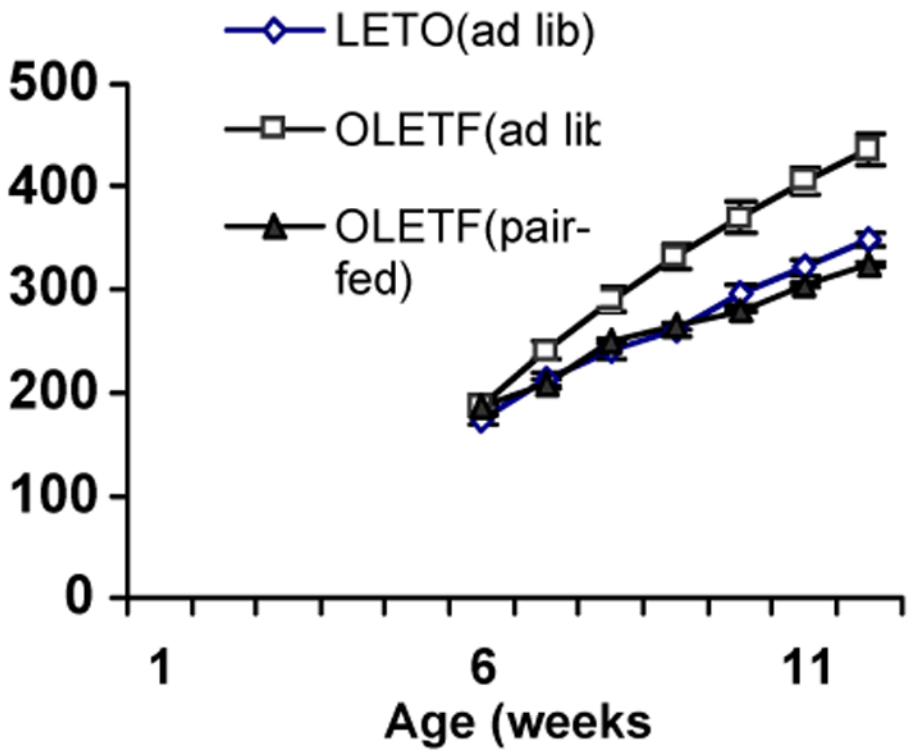

Figure 2.
Effect of pair feeding on body weight gain in OLETF rats. Restricting OLETF rats intake to the levels of LETO controls prevents their obesity.

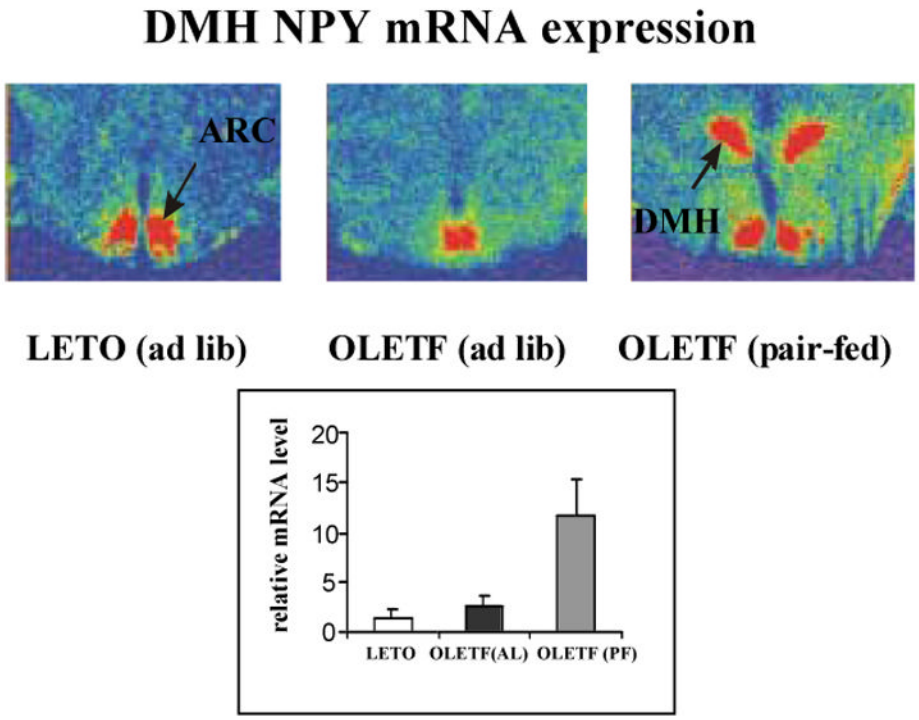

Figure 3.
Effect of par feeding on hypothalamic NPY mRNA expression. Pair feeding normalizes arcuate nucleus (ARC) NPY mRNA levels but results in a significant increase in dorsomedial hypothalamic (DMH) NPY mRNA expression. Representative color enhanced photomicrographs of in situ hybridization in top panels. Quantitative representation of the data is shown in the lower panel.

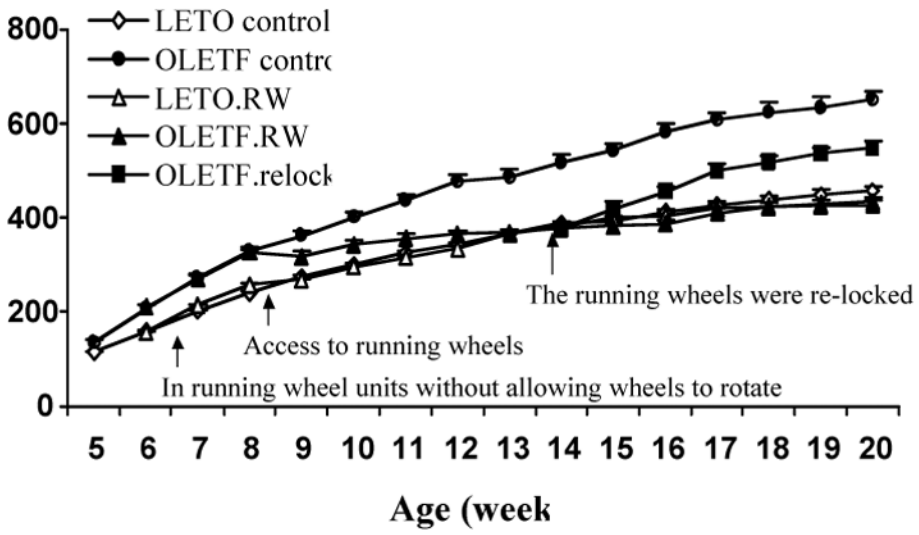

Figure 4.

Effects of running wheel access on body weight in LETO and OLETF rats. Exercise has no significant effect on rates of weight gain in LETO rats (LETO.RW). However, exercise normalizes body weight in OLETF rats (OLETF.RW). Lower body weights are maintained while rats have running wheel access. Relocking the running wheels (OLETF.relocked) results in increased body weight but not to levels of sedentary OLETF rats (OLETF conrol).

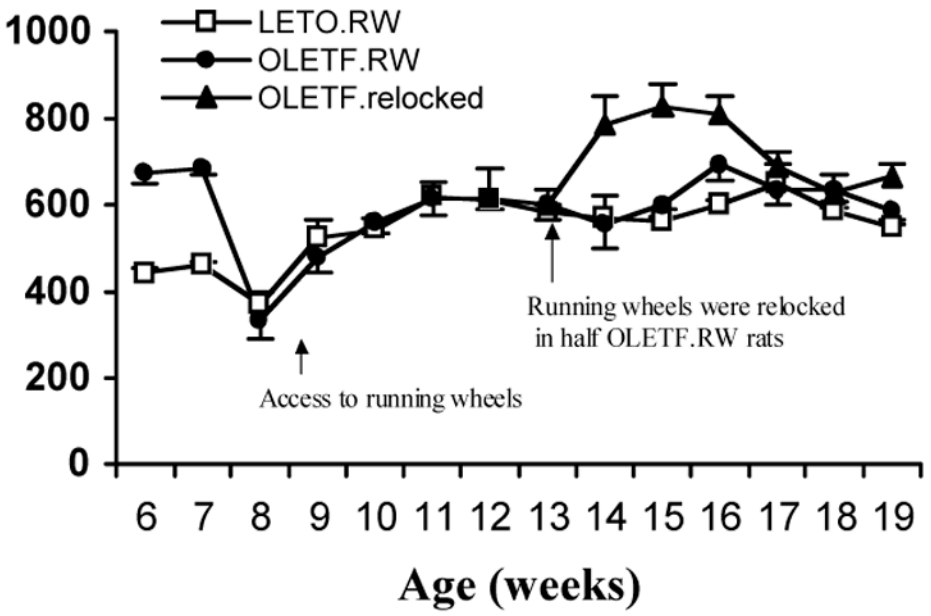

Figure 5.

Effects of running wheel access on food intake in LETO and OLETF rats. Exercise results in a transient decrease in food intake in LETO rats (LETO.RW). This decrease is followed by a longer term increase in food intake in response to the increased energy expenditure of exercise. Exercise normalizes food intake in OLETF rats (OLETF.RW). When running wheels are relocked, OLETF rats' food intake transiently increases (OLETF.relocked). When body weight stabilizes, food intake falls.

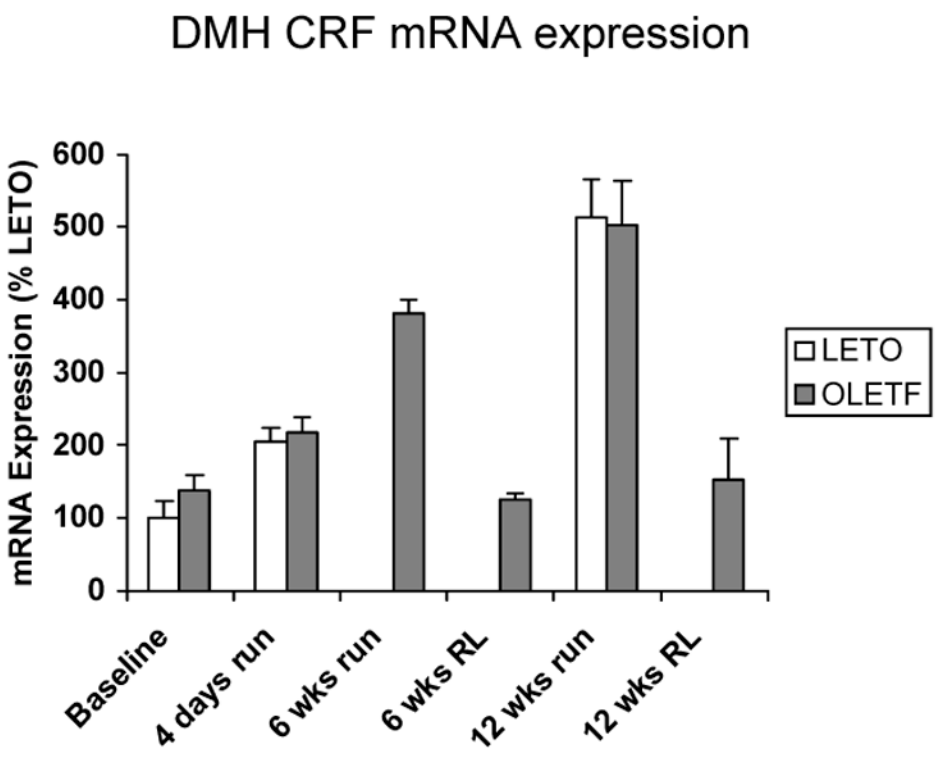

Figure 6.
Effects of running wheel access on DMH CRF mRNA expression in LETO and OLETF rats. Exercise increases DMH CRF mRNA within four days of running wheel access in both OLETF and LETO rats and levels continue to increase in proportion to the duration of running wheel access. Relocking the running wheels normalizes DMH CRF mRNA within 4 days (6 week RL) and levels remain low (12 week RL) in OLETF rats with locked wheels.

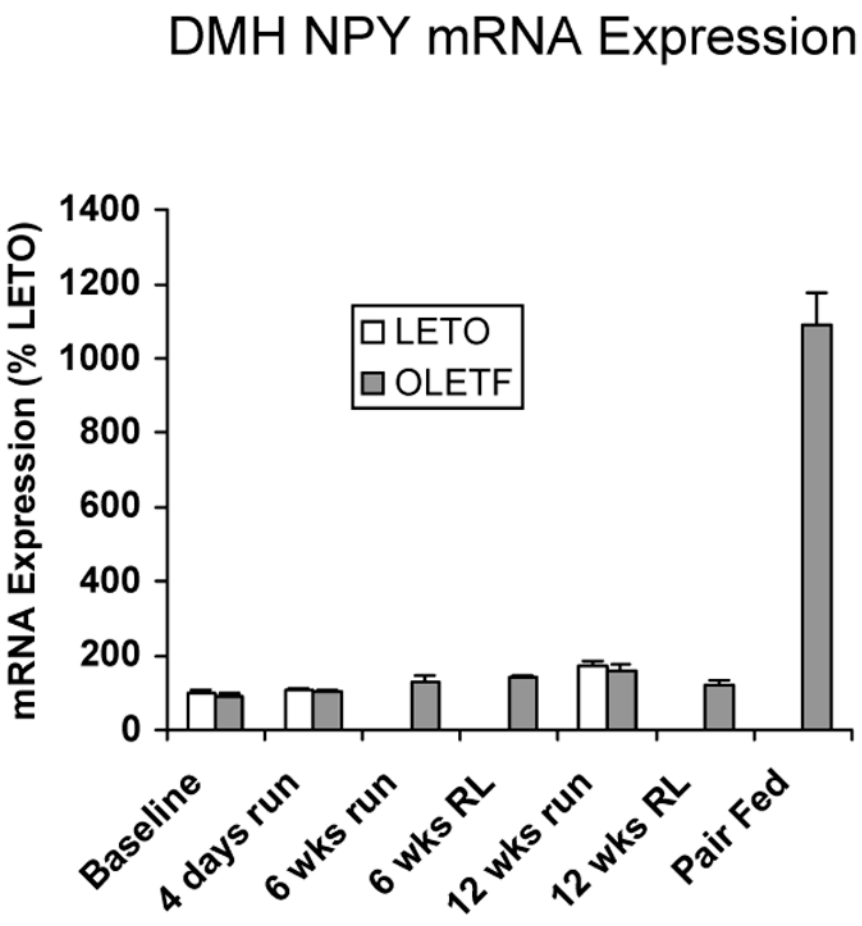

Figure 7.
Effects of running wheel access on DMH NPY mRNA expression in LETO and OLETF rats. Exercise does not alter DMH NPY at short term timepoints (4 days run, 6 wks run) but results in small but significant increases in DMH NPY in both groups at the 12 week timepoint. DMH NPY expression levels are not elevated in OLETF rats for whom running wheels have been relocked. Exercise induced weight normalization in OLETF rats occurs without elevations in DMH NPY mRNA comparable to those iin rats that were weight normalized by pair feeding. Thus exercise exerts a lasting inhibitory control on DMH NPY mRNA expression.