Published in final edited form as:

Curr Opin Behav Sci. 2018 October ; 23: 160–170. doi:10.1016/j.cobeha.2018.06.014.

Functional and structural plasticity contributing to obesity: roles for sex, diet, and individual susceptibility

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Abstract

The role of cortico-striatal pathways in cue-triggered motivational processes have been extensively studied. However, recent work has begun to examine the potential contribution of plasticity in these circuits to obesity. Despite the inclusion of women in human obesity studies examining neurobehavioral alterations in cue-triggered motivation, preclinical studies have focused mainly on male subjects. This lack of female subjects in preclinical research had led to a gap in the basic understanding of the neural mechanisms underlying over-eating in females. In this review, we highlight recent work from our lab and others that has begun to elucidate how diet, obesity, and individual susceptibility to weight gain influence functional and structural plasticity within the nucleus accumbens and prefrontal cortex in adult rats. As is the case throughout neuroscience, studies of females or sex differences are largely lacking in this area. Thus, below we describe preliminary neurobehavioral results from female studies in our labs and point out areas for future investigation.

1 Introduction:

It is well-established that sights, sounds, and smells that are associated with food (i.e., food cues) can influence feeding behavior. For example, priming with a food cue can induce feelings of hunger and craving, bias food choice, and result in consumption of larger portions of food in people [1,2]. The neural mechanisms underlying cue-triggered motivation have been studied extensively and rely in large part on activity within prefrontal cortex (PFC), amygdala (Amy), and the nucleus accumbens (NAc; [3–7]). Work in this broad area has been integral for understanding the fundamental neurobiology of feeding and motivation. However, how neurobehavioral processes underlying food craving and seeking are affected by consumption of diets rich in sugars and fats, and by physiological alterations

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accompanying obesity are poorly understood. Furthermore, while human studies often include females, preclinical studies needed to understand causal and mechanistic relationships have largely focused on males.

Human studies have shown that behavioral and neural responses to food cues differ dramatically in obese vs. lean individuals [8–11]. For example, obese people report stronger food craving and eat larger portions when primed with food cues [12,13]. In addition, the magnitude of activations in the NAc and PFC in response to food cues are stronger in overweight and obese, compared to healthy weight people [14–16]. Thus, these correlation observations suggest that obesity may produce alterations in brain regions responsible for motivational responses to food cues that likely hamper weight loss. In addition, the magnitude of increases in the fMRI BOLD signal in the NAc triggered by food cues predicts future weight gain in healthy weight people and future inability to lose weight after obesity [17–19], suggesting that enhanced responsivity of these circuits may be a cause, rather than consequence of obesity. Despite the increased risk for poor health outcomes in obese vs. healthy weight women [20–22], relatively few preclinical studies have examined the impact that sex may have on cue-triggered craving, the underlying neural mechanisms, or the potential influence of the reproductive cycle (see [23] for discussion). Human studies have found that in the fasted state functional connectivity between the amygdala and dorsomedial PFC is greater in obese women vs. obese men [24]. In addition, in adolescent girls, the magnitude of activations in the PFC and NAc triggered by food cues is positively correlated with future weight gain [19,25,26]. Thus, although enhanced neurobehavioral responses to food cues have been found in both males and females [26–29], direct examination of sex differences and/or roles for gonadal hormones in modulating cue-triggered motivation remain poorly understood. Nonetheless, the human literature suggests that there are interactions between individual differences in neurobehavioral responsivity to food cues, susceptibility to obesity, and effects of fatty, sugary diets on motivation. Of course, distinguishing cause from effect is difficult without the use of preclinical models. Therefore, in this review, we highlight recent work from our lab and others that has begun to elucidate how diet, obesity, and individual susceptibility to weight gain influence glutamatergic plasticity underlying cue-triggered motivation in rodents. As is the case throughout neuroscience, studies of females or sex differences at the preclinical level are largely lacking in this area. Thus, below we describe preliminary neurobehavioral results from female studies in our labs and point out areas for future investigation.

2 Basal differences in cue-triggered motivation in models of individual susceptibility to obesity:

There is a substantial animal literature on the neurobiology of cue-triggered motivation (i.e., incentive motivation), its role in food-seeking, and the influence of hunger and satiety on these behaviors. However, the literature examining effects of calorie dense foods and obesity on these behaviors and how these experiences interact with susceptibility to obesity is only beginning to emerge. One way to model individual susceptibility to obesity in rodents is to conduct initial behavioral testing and then subsequently identify obesity susceptible rats based on weight gain when given free access to a moderately fatty diet¹ (~19–25%). Under

these conditions, some Sprague Dawley rats rapidly gain a substantial amount of weight and fat mass, while others stay on a similar weight gain trajectory as animals given standard lab chow [30]. Behavioral data collected prior to diet manipulation can then be examined post hoc to determine relationships between food intake, weight gain, and baseline behavior. Using this approach, we found that the magnitude of cue-triggered approach to the place of expected food delivery was greater in male rats that were subsequently identified as susceptible to weight gain (i.e., “gainers”) compared to those rats who gained less weight (i.e., “non-gainers”; [31]). This is consistent with human studies described above and supports the idea that there are basal differences in neural systems mediating incentive motivation in obesity susceptible vs. resistant populations.

Using weight gain to identify sub-populations as described above precludes examination of basal neural differences. In addition, diet-induced obesity is less pronounced in female vs. male rats, and fat storage itself is influenced by ovarian hormones [32]. Thus, a complementary approach is to use rats that have been selectively bred for their propensity or resistance to weight gain [30,33]. Importantly, in humans, weight is a heritable trait [34], and obesity is polygenic and influenced by early life experiences (see [35] for review). Similarly, obesity in this selectively bred model (originally developed from Sprague Dawley rats) is polygenic and influenced by early life experiences [36,37]. Figure 1 shows % weight gain in female and male rats from selectively bred obesity-prone and obesity-resistant lines. Differences in weight gain of female obesity-prone vs. obesity-resistant rats given standard lab chow (Lab Diet 5001: 4 kcal/g; 4.5% fat, 23% protein, 48.7% carbohydrates; % of caloric content) are modest (Fig. 1A). However, consumption of a sugary, fatty, “junk-food” diet (4.5 kcal/g; 19.6% fat, 14% protein, 58% carbohydrates; % of caloric content [31]; produces marked increases in weight of obesity-prone but not obesity-resistant females (Fig. 1A). Patterns in males are generally similar, though more pronounced than in females (Fig. 1C). These differences in weight gain are due in part to greater food intake (Fig. 1B females; Fig. 1D males) and increased adiposity in obesity-prone vs. obesity-resistant rats (unpublished observation, CRF and YAC).

We recently conducted behavioral studies to determine whether there are basal differences in cue-triggered approach between females from these established obesity-prone and obesity-resistant lines. Furthermore, while previous studies have established that naturally occurring elevations in estradiol decrease food intake [38,39], and that estradiol treatment in ovariectomized females is sufficient to decrease food intake and body weight [40,41], how the cycle affects cue-triggered motivation is unknown. Thus, we also determined how cue-triggered approach varied across the cycle in intact females.

We found that the magnitude of cue-triggered approach (tested in the absence of food itself) was greater in obesity-prone vs. obesity-resistant females (Alonso-Caraballo and Ferrario, 2018). This is consistent with effects described above, and stronger Pavlovian-to-instrumental transfer (PIT) in obesity-prone vs. resistant males [42]. In addition, in obesity-prone females the magnitude of approach behavior was higher during metestrus/diestrus (when estradiol is relatively low) compared to proestrus/estrus (when estradiol is elevated).

¹In studies described below, rats are given free access to diets in their home cage, unless otherwise specified.

In contrast, behavior was stable across the cycle in obesity-resistant rats. Furthermore, hormonal replacement (4 cycles of estradiol followed by progesterone; as in [43]) in ovariectomized females was sufficient to reduce cue-triggered approach in obesity-prone and outbred rats, but not obesity-resistant rats. These data demonstrate a role for ovarian hormones in modulating cue-triggered food-seeking behaviors in both outbred and obesity-prone rats. In addition, the absence of effects in obesity-resistant rats raises the intriguing possibility that resistance to weight gain may be linked to an absence of hormonal regulation of cue-triggered motivation. Taken as a whole, data from females and males show that there are inherent differences in incentive motivation that co-vary with susceptibility to weight gain. This model also provides a tool to differentiate basal vs. diet- or obesity-induced changes in the neural systems mediating these behaviors (see also section 3 below).

3 Effects of sugary, fatty, “junk-foods” and diet-induced obesity in the NAc:

While many studies have examined how diets rich in fat and sugar alter mesolimbic dopamine systems that influence motivation [44–47], glutamatergic transmission within the NAc also plays critical roles in cue-triggered motivation [47–49]. For example, amygdalar inputs to the NAc are necessary for the expression of cue-triggered food-seeking in the form of PIT [50,51] and NAc AMPARs blockade is sufficient to prevent the expression of PIT in obesity-prone males [42]. Furthermore, excitatory transmission in the core and shell sub-regions of the NAc play different roles in consummatory vs. food-seeking behavior. For example, antagonism of AMPARs in rostral NAc shell, but not core, increases food consumption outside the home cage [52,53]. In contrast, AMPAR transmission in the NAc core has been most tightly linked to cue-triggered motivation for both food and drug reinforcers [47,49,54]. Craving for and consumption of calorie dense foods is often initiated by food cues. Thus, determining diet and obesity-induced alterations in NAc excitatory transmission may shed light on the mechanisms underlying overeating and obesity.

3.1 NAc excitatory transmission:

In regard to diet-induced alterations, consumption of foods high in sugar, fat, or a combination of the two, regardless of obesity, is sufficient to enhance NAc core AMPAR-mediated transmission and expression in outbred male Sprague Dawley rats ([55–57]; similar studies in females have yet to be published). For example, repeated ingestion of sucrose outside the home cage increases NAc core AMPAR protein expression and synaptic transmission within minutes following the last session of sucrose consumption [57]. In this same study, similar effects on AMPAR protein expression were found following saccharine consumption, suggesting that increases are not linked to caloric density.

Two studies to date have examined interactions between individual susceptibility to obesity and effects of palatable food on NAc excitatory transmission. Brown et al. [58], found increases in the AMPA/NMDA ratio in the NAc core of male outbred rats who became obese on a 45% high-fat diet compared to rats given the same diet that did not become obese. In studies using selectively bred lines, we have found larger increases in NAc core AMPAR expression and function following consumption of sugary, fatty foods in obesity-

prone vs. obesity-resistant males [42,56]. Specifically, 10 days of “junk-food” consumption [56] or sucrose exposure during instrumental and Pavlovian training [42] without obesity was sufficient to induce NAc glutamatergic plasticity in obesity-prone but not obesity-resistant rats. Thus, obesity or metabolic dysregulation do not appear to be required to induce alterations in NAc excitatory transmission, at least in males. This is also consistent with increases in excitatory transmission following sucrose or high-fat consumption in the absence of weight gain [55,57,59]. Thus, data from selectively bred and outbred males are consistent with the idea that enhanced activity in the NAc may be a cause rather than a consequence of obesity. Of course, this does not rule out the possibility of additional obesity-induced alterations in NAc function. Finally, although similar studies in females have yet to be published (see section 3.3 below), sex differences are likely given that dendritic spine density (an indirect indicator of excitatory synaptic contacts) in the NAc core is greater in intact females in the proestrus phase compared to males [60]. Thus, it will be important to determine how sugary, fatty food consumption affects excitatory transmission in intact females, and how ovarian hormones may influence diet-induced plasticity.

Behaviorally, diet-induced increases in NAc AMPAR expression and transmission in outbred males have also been associated with the “incubation of high-fat craving” [55]. “Incubation of craving” refers to a time-dependent increase in food-seeking in the presence of food cues, but the absence of food itself [61]. Dingess et al. [55], found increases in the AMPA/NMDA ratio in the NAc core of male outbred rats that emerged with behavioral incubation. These data are consistent with a study showing enhanced food-seeking following high-fat diet consumption in those rats who became obese [58]. In contrast, the incubation of sucrose craving has been associated with a reduction in AMPA/NMDA ratio [62]. The simplest explanation for these opposite effects is the different types of food consumed (fats vs. sucrose). However, consumption of sucrose, saccharine, or diets composed of a mixture of sources of nutritive value (e.g., junk-food diet described above) have all been shown to produce increases in NAc excitatory transmission. Thus, it’s likely that interactions between the circumstances around food consumption (e.g., instrumental response contingency, pairing of food with discrete cues, given freely in the home cage, etc.) and the type of food itself may influence the net effect on NAc excitatory transmission. Finally, studies in females are lacking. Given behavioral similarities in cue-triggered motivation in males and females, it is reasonable to suspect that similar mechanisms may be involved. However, recent studies in the learning literature have shown that this intuition is not always correct, as similar behaviors can be mediated by different mechanisms in males and females (e.g. [63,64]).

3.2 AMPAR subpopulations:

The nature of food-induced changes in AMPAR function described above is influenced by individual susceptibility and may vary between males and females. Specifically, junk-food diet consumption increases the expression and function of NAc core calcium-permeable AMPARs (CP-AMPA) in obesity-prone, but not obesity-resistant male rats [56] and blockade of NAc core CP-AMPA transmission is sufficient to block incentive motivation in male obesity-prone rats [42]. To our knowledge, no studies to date have examined effects of diet on NAc excitatory transmission or glutamate receptor expression in females (outbred or

otherwise). However, preliminary data from our lab suggest one month of free access to junk-food followed by 14 days of junk-food deprivation results in a reduction in GluA1 and GluA2 surface expression in the NAc (core and shell combined) of obesity-prone, but not obesity-resistant females. This pattern is suggestive of a decrease in GluA1/2-containing AMPARs, whereas increases in GluA1 surface expression in males has been associated with the up-regulation of CP-AMPA (GluA1/1 or GluA1/3; [56,65]). One caveat to note is that in males AMPAR expression was evaluated after a one-month junk-food deprivation period while females were tested at deprivation day 14. However, electrophysiological studies in males have found increases in CP-AMPA at deprivation day 14, suggesting that protein expression may also be elevated at that time. In addition, females in these preliminary studies were naturally cycling. Thus, there may be additional effects of hormonal changes [66]. Nonetheless, preliminary data suggest that effects of diet on NAc AMPARs likely differ in males and females and highlight the need for additional studies in this area.

3.3 Dendritic Morphology:

Alterations in glutamatergic transmission are often accompanied by changes in the structure and number of excitatory synapses [67–69]. Indeed, a wide range of stimuli including environmental enrichment [70], social isolation [71], salt appetite [72], and exposure to drugs of abuse [73] can induce persistent structural changes in dendritic branching and spine density in the NAc and PFC. These structural changes are thought to reflect experience induced plasticity of glutamatergic synaptic transmission that influences motivation [5]. In females, administration of estradiol decreases dendritic spine density [74] and reduces mRNA for the GluA2 subunit in the NAc [66], demonstrating roles for ovarian hormones in structural and glutamatergic plasticity. While the relationship between structural plasticity and drug addiction has received substantial attention [73,75], relatively few studies have examined the capacity for food to induce structural plasticity, and even fewer have examined potential sex differences.

Data from our laboratory has shown that self-administration of high-fat food pellets alters dendritic spine morphology in the NAc of males [55]. These effects vary by NAc core and shell sub-regions and emerge with the incubation of craving described above. Specifically, instrumental responding was greater 30 days compared to 1 day after cessation of high-fat self-administration (i.e., incubation); this was accompanied by an increase in the density of mushroom shaped spines within the NAc core at day 30 but not day 1. No effects were observed in the NAc shell after cessation of high-fat self-administration. Increases in the number of mushroom shaped spines are indicative of increases in mature glutamatergic synaptic inputs to the NAc [76–78] and are consistent with increases in NAc AMPAR-mediated transmission described above [79]. Interestingly, changes in morphology in NAc core were not observed when rats were given free access to this same high-fat diet in their home cages [80]. This suggests that consumption of high-fat alone is not sufficient to enhance synaptic contacts in this region, but rather that circumstances surrounding instrumental self-administration (e.g., relatively restricted access, presence of food cues, etc.) or a period without access to the diet may be particularly important for driving the changes observed in the incubation model.

Rats allowed to work for grain food pellets (and associated cues) also showed behavioral incubation and increases in the density of mushroom shaped spines within the NAc core and shell [55]. While these pellets had a similar macronutrient profile as standard home cage lab chow, they differed in texture and ease of consumption. Thus, the relative novelty of the food reinforcers, its intermittency, and their accompaniment by discrete cues in self-administration settings appear to strongly influence incubation and associated neural alterations [81]. To date, similar studies have not been conducted in females. However, behaviorally females show the “incubation of craving” phenomenon following withdrawal from psychostimulant drugs [82,83] and some data suggest the magnitude of this behavior may vary with the cycle [84]. Furthermore, although the mechanisms have not been determined, acute estradiol treatment decreases dendritic spine density in the nucleus NAc core [74]. Thus, increases in estradiol would be predicted to reduce the incubation effect following food or drug self-administration; this would also be consistent with effects of ovarian hormones on conditioned approach described above. Of course, studies directly testing these hypotheses are necessary.

3.4 Summary NAc:

The data from males described above suggests that consumption of sugary, fatty foods induces long-term potentiation at glutamatergic synapses in the NAc (though see also, [62]). This is predicted to enhance excitatory drive to the NAc and is consistent with stronger incentive motivation and more persistent food-seeking behavior described above.

Although parallel studies in females have not been conducted, preliminary data suggest that diet manipulation may also enhance excitatory transmission in females, but that different AMPA receptor populations may be recruited in females.

4. Effects of sugary, fatty, “junk-foods” and diet-induced obesity in the PFC:

In addition to effects on the NAc, consumption of sugary, fatty foods also produces alterations in PFC regions including the prelimbic (PL), infralimbic (IL), and orbital frontal cortex (OFC; [85]). Activity in these regions influences many aspects of behavior including initiation and inhibition of food-seeking by the PL and IL regions, respectively [86,87], and modification of goal-directed behavior by activity in the OFC [88]. In addition, glutamatergic afferents from the PFC innervating the NAc influence motivated behaviors. For example, inducing long-term depression of these synapses can reduce “incubation of craving” for cocaine [89]. Consequently, the PFC and NAc work in concert to influence behavioral output.

4.1 Morphology:

In the same study described above, Dingess et al. [80], demonstrated that high-fat diet consumption induces structural changes within the mPFC that are independent of weight gain. Specifically, a reduction in the density of thin spines within the IL-PFC was found following 21 days of high-fat access. This may reflect a loss in the potential to produce new synapses or a conversion of immature synapses to a mature state [76,78,79]. In tissue from

these same rats, no changes were observed in the PL-PFC. Similar effects were found when high-fat was given ad libitum in the home cage or self-administered [80]. This work suggests that exposure to high-fat may specifically impact the excitatory drive from the IL-PFC to the NAc, which may perturb the ability of the IL-PFC to curb food-seeking behaviors, at least in males. Whether similar effects are found in females, or in obesity-prone vs. obesity-resistant rats is currently unknown.

It is useful to compare and contrast effects of pharmacological reinforcers (like psychostimulant drugs) to ethologically relevant reinforcers like food because psychostimulant drugs engage and alter the function of neural systems that mediate food-seeking and feeding behavior. To our knowledge, only one study directly compared effects of sucrose consumption on spine density to that of self-administered amphetamine. They found that while amphetamine increased spine density in the NAc and mPFC, sucrose instead resulted in increases within the OFC relative to untreated controls [90]. This suggests that natural vs. pharmacological reinforcers produce distinct structural alterations in these circuits that may differentially govern food- and drugseeking behaviors. However, there is also evidence for mechanistic overlaps between enhanced food- and drug-seeking behaviors. For example, cocaine craving is also associated with time-dependent increases in NAc dendritic spine density and CP-AMPA up-regulation [91], and there is cross-sensitization between food and drug rewards [31,92]. Furthermore, incubation of cocaine craving also involves the maturation of silent synapse specifically in PL-PFC to NAc core projections [93]. However, whether similar mechanisms are involved in the incubation of high-fat craving, and potential sex differences in these effects have not yet been determined.

In addition to studies of the PFC described above, Dr. Borgland's research group has found decreases in basilar spine density and branch complexity in lateral OFC after male mice were given extended access to a "cafeteria diet" [94]. Consistent with the role of OFC in modifying goal-directed behaviors, high-fat and high-sugar diets can reduce goal directed behavior [58], while high-fat has been shown to enhance impulsivity mediated by prefrontal cortical regions [95]. Similar to effects described above, diet-induced increases in impulsivity did not require weight gain or obesity. To our knowledge no similar studies have been conducted in females (though see section 4.2), and distinctions between effects due to diet vs. obesity on OFC neuronal morphology have not been made.

4.2 PFC Interneurons:

Activity of parvalbumin containing fast-spiking interneurons (FSI) within the PFC influences the firing of pyramidal neurons, thereby tuning and organizing activity within the PFC. Our unpublished preliminary results (Figure 2) suggest that there are distinct interactions between high-fat diet consumption, sex, and susceptibility to obesity that influence excitability of FSI within the PL-PFC. Specifically, in females but not males FSI spike number was higher in obesity-prone vs. obesity-resistant rats given chow (Fig 2B, D). Following high-fat diet, FSI spike number was reduced in female obesity-prone rats compared to their chow fed counterparts, while diet did not affect FSIs spike number in obesity-resistant females (Fig. 2B). We speculate that the diet-induced decrease in obesity-prone females may reduce GABAergic tone from FSIs onto local pyramidal neurons,

thereby enhancing activity of pyramidal neurons in the PL-PFC [96]. In contrast, high-fat did not alter FSI spike number in obesity-prone males, suggesting that there are sex differences in diet-induced changes within the PFC (Fig. 2D), and possibly in PFC projections to other regions such as the NAc and amygdala. Additional studies examining these possibilities are underway; effects in IL-PFC are yet to be determined.

4.3 Summary PFC:

The picture that is emerging from studies of the PFC is one of distinct structural and organizational differences in specific sub-regions that vary by food type, sex, and susceptibility. Although complex, continued examination of these factors using a variety of models is needed to distinguish causes of overconsumption that drive obesity from effects of food consumption and physiological alterations that accompany obesity.

4.4 Integration of effects in PFC and NAc:

As described above, enhanced NAc glutamatergic transmission contributes to stronger cue-triggered food-seeking behaviors that often initiate and spur on feeding. This plasticity appears to be influenced by experiences surrounding food consumption (e.g., novelty of environment, food itself, and association of discrete cues with consumption). In contrast, consumption of calorie dense foods alone is sufficient to induce changes in cortical regions [55,80]. Thus, we speculate that changes in the PFC induced by consumption of calorie dense foods may compound alterations in neurobehavioral responses to specific food cues. For example, diet-induced reductions in FSI activity may result in hyperactivity of the pyramidal neurons within the PL-PFC and increase glutamatergic input from the PL-PFC to the NAc core. This combination may allow food cues to gain a disproportional ability to drive craving, ultimately leading to increased consumption, weight gain, and a reduced ability to curb unhealthy eating.

5. Future Directions & Summary:

While the neurobiological mechanisms underlying basal and diet-induced alterations in motivation are likely complex, current data support a role for alterations in both glutamatergic and dopaminergic transmission within reward circuits (for review, [97–99]). Relatively few studies have been done in this area, thus it is unknown how different pathways within motivational circuits (e.g., direct vs. indirect pathways in striatum, cortical vs. amygdalar input to the NAc) may be affected. Above we have focused on excitatory transmission, dietary effects that precede obesity, and alterations that mediate cue-triggered food-seeking behaviors because this is the earliest potential point of intervention and may help address the difficulty of maintaining a healthy weight over long periods of time. However, while anticipation of food has been associated with enhanced striatal activity, responses to the acute ingestion of food have been associated with blunted neurobehavioral responses. For example, in obese humans striatal responses to ingestion of palatable food are lower compared to healthy weight individuals (see [100,101]; for review), consistent with blunted hedonic responses to oral sucrose following obesity in preclinical models [31]. The neural mechanisms underlying these reduced responses to food consumption are poorly understood. There is some evidence that reduced expression of striatal D2 dopamine

receptors may contribute [102,103], although high-fat consumption has also been shown to enhance sensitivity to the behavioral effects of the D2 dopamine receptor agonist quinpirole in males ([104]. Interestingly, this was not the case in females; in a separate study from this same research group, high-fat consumption did not affect sensitivity to quinpirole [46]. Thus, here again sex differences are poorly understood.

With the exception of a few, many studies described above did not differentiate between effects due to fat or sugar consumption versus those due to weight gain or obesity. This is an important distinction to make because the causes of obesity must not necessarily precede obesity and its accompanying metabolic dysregulation. For example, in outbred males consumption of high-fat or junk-food diets in the absence of obesity reduces impulse control and enhances conditioned approach [95,105]. These diet-effects may shed light on the recurrence of obesity after periods of healthy weight maintenance.

Given the morphological and functional changes in PFC following diet manipulations, and the role of the PFC in food-seeking, future studies specifically examining changes in excitatory transmission in PFC inputs to the NAc are needed. This is important because different circuits may be altered by diet-manipulation vs. weight gain, thereby dramatically altering the net effect on behavior. Furthermore, high-fat diets do not necessarily produce the same alterations as high-sugar diets, or diets using a combination of the two (e.g., neuroadaptations associated with incubation of high-fat vs. sucrose craving discussed above). This also highlights the need for a diverse approach to studying obesity that considers sex, macronutrient composition, weight gain, and metabolic dysregulation in order to distinguish the neurobehavioral drivers of obesity from its consequences.

In summary, food cues differentially impact food-seeking in obesity susceptible and resistant people. The preclinical data summarized above suggest that this may be due to an intrinsic enhancement of the incentive motivational properties of food cues in obesity-susceptible vs. resistant populations. These individual differences may then be compounded by diet-induced alterations in PFC and NAc function that further promote food-seeking behaviors [105]. Effects of obesity, diet, and individual susceptibility to obesity in females have been largely overlooked in the preclinical literature. The few studies conducted in females suggest that although there are behavioral similarities, the same diet manipulation may produce different neural outcomes in females and males [97,106]. Regardless of overt sex differences, preclinical studies in females are necessary to gain a complete understanding of the drivers of the current obesity epidemic.

Acknowledgements:

This work was supported by NIDDK R01DK106188 to CRF and NIDA R01DA040965 to TEB; YAC was supported by NIDDK R01DK106188–02-S1.

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expression of cue-triggered food-seeking only in obesity-prone rats. These data support the idea that susceptibility to obesity is accompanied by stronger incentive motivational responses to food cues prior to the development of obesity, and that this behavioral response is mediated by glutamatergic plasticity within the NAc.

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both chow and high-fat groups 30d after training within the nucleus accumbens core, which was accompanied by an increase in the AMPA/NMDA ratio. The authors concluded that operantly responding for food rewards, independent of macronutrient composition, induced synaptic strengthening within the nucleus accumbens core, which may underlie cue-induced food seeking behaviors. However, consumption of dietary high-fat specifically modified the infralimbic region of the prefrontal cortex, a region important for curbing behavior. Therefore, this paper suggests that food cues induce seeking behaviors independent of reward value and animals that have been previously exposed to high-fat have altered cortical activity, which could interfere with the animal's ability to properly regulate consumption of palatable foods and predispose them to obesity.

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Female rats

Male rats

Figure 1.

Effects of junk-food on weight gain and food intake in obesity-prone (OP) and obesity-resistant (OR) rats (N=8 rats per group). Weight gain (A) and food intake (B) measured weekly in females given free access to a junk-food (JF) or a chow (CH) diet in the home cage for 1 month. Weight gain (C) and food intake (D) measured weekly in males given free access to JF or CH diets in home cage for 1 month. As expected, OP females given JF were heavier and consumed more calories than any other group. In addition, weight and food intake were similar between OP and OR chow fed females. In males, OPs and ORs given JF were heavier than their chow fed counterparts, and OPs weighed more than ORs. Unlike females, OP males given chow were heavier than OR males on chow. Although, it should be noted that weight does not always accurately reflect increases in fat mass, these data highlight sex differences in weight gain in this model.

Figure 2.

Preliminary data showing the effects of high-fat diet on firing patterns of fast spiking interneurons (FSI) in the prelimbic prefrontal cortex of obesity-prone (OP) and obesity-resistant (OR) female and male rats. A) Percent weight gain in females given free access in the home cage to chow (CH) or 60% high-fat (HF; OP CH n=4, OP HF n=3, OR CH n=3, OR HF n=3). B) Number of action potentials in FSIs from females in response to increasing current injections (100 to 800 pA; N=cell #/animal#; OP CH n=9/4, OP HF n=12/3, OR CH n=10/3, OR HF n=13/3). Initial results suggest that consumption of high-fat diet results in a reduction in the number of action potentials in OP females, but not OR females. In addition, differences in baseline FSI firing rate are apparent between OP CH and OR CH groups. C) Percent weight gain in males (OP CH n=3, OP HF n=4, OR CH n=4, OR HF n=4). D) Number of action potentials in FSIs from males in response to increasing current injections (–100 to 800 pA; OP CH n=12/3, OP HF n=13/4, OR CH n=15/4, OR HF n=18/4). In males, there was a trend towards a reduction in the number of action potentials in both OP and OR rats that consumed dietary high-fat. However, these differences were not as apparent as those seen in females. In addition, no baseline differences in FSI firing rate were apparent in males. Insets show example traces in response to 600pA of current injection from a representative cell in each group; scale bar represents 20mV and 20ms.