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The Effects of Overfeeding and Propensity to Weight Gain on the Neuronal Responses to Visual Food Cues

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Abstract

Obesity is a serious and growing public health problem in the United States and the world. The pathophysiological processes that underlie the increasing prevalence of obesity have not been clearly defined but likely involve faulty interactions between environmental factors, which favor positive energy balance, and weight regulatory systems in genetically susceptible individuals. Individuals who are genetically predisposed to thinness in the current environment may be able to sense and respond to excess energy intake more rapidly and accurately than those predisposed to obesity. The regulation of energy intake and therefore the potential adaptation to changes in energy balance is a complex process with interactions between homeostatic and non-homeostatic signals likely being critical. We have observed that thin (obese-resistant) individuals quickly sense changes in positive energy balance with not only changes in measures of appetite but also in brain regions important for the regulation of energy intake. This is in contrast to reduced-obese (obese prone) individuals who do not appear to appropriately sense the changes in positive energy balance, suggesting that there is a differential sensitivity to positive energy balance between obese-resistant and obese-prone individuals. We have also found evidence for important interactions between external food cues and activation of brain regions important in the homeostatic regulation of energy balance. These findings emphasize the important role of environmental visual cues and suggest that there are important phenotypic differences in the interactions between external visual sensory inputs, energy balance status, and brain regions important in the regulation of energy intake.

Keywords

fMRI; neuroimaging; hunger; satiety; thin; hypothalamus

1. Introduction

Obesity is a serious and growing public health problem. Despite efforts to promote healthy eating and physical activity behaviors in Americans, the prevalence of obesity and related metabolic disorders such as diabetes continue to increase [1]. A majority of Americans are either overweight or obese leaving only a minority with a “normal” body mass index (BMI). While genes undoubtedly play an important role in the development of obesity, this dramatic

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increase in the prevalence of obesity has occurred over a relatively short period of time in history. Genetic influences would not be expected to change over such a short period of time, suggesting that environmental factors are likely to be playing a significant role in the cause of this epidemic. The Institute of Medicine concluded in 1995 that “there has been no real change in the gene pool in this period of increasing obesity. The root of the problem, therefore, must lie in the powerful social and cultural forces that promote an energy-rich diet and a sedentary lifestyle” [2]. Some authors have even suggested that weight gain is a “normal” response to the modern environment [3], while others call the current environment “toxic” for those with a predisposition to becoming obese [2]. We believe that one of the most dramatic changes in the environment over the last 40 years has been the broad availability of relatively inexpensive highly palatable foods leading to excessive energy intake, and it is almost certain that most people in the United States experience at least brief periods of positive energy balance produced by the over-consumption of highly palatable food combined with periods of low levels of physical activity.

1.1 Thinness in the Current Environment

Physiologic feedback mechanisms appear to be primarily in place to protect the organism during states of undernutrition, so an obvious question that arises is why or how do some people remain thin in the current environment? Clearly some individuals maintain a healthy weight in the face of an environment that promotes weight gain. It may be that genetically determined biological systems that regulate weight function differently or more effectively in thin individuals as compared to those predisposed to weight gain. In other words, thin individuals appear to respond to these brief periods of positive energy balance with adaptive responses that promote a return to baseline weight, while most people (weight gainers) appear to have less appropriate responses to positive energy balance and gradually gain weight and accumulate fat mass. If this is true, then identifying the unique aspects of how weight is regulated in thin individuals could provide important information on pathways that could be therapeutic targets in obese individuals. In addition, a number of studies suggest that thinness is at least as genetically determined as obesity and perhaps even more so [4-6].

1.2 Adaptations to the Obesigenic Environment

The pathophysiologic processes that underlie the increasing prevalence of obesity have not been clearly defined but likely involve faulty interactions between environmental factors, which favor positive energy balance, and weight regulatory systems in genetically susceptible individuals. Individuals who are genetically predisposed to thinness in the current environment must therefore adapt to times of positive energy balance more rapidly and accurately than those predisposed to weight gain. Adaptations could occur with changes in energy expenditure, substrate metabolism, and/or energy intake. There is no clear evidence that either resting energy expenditure or the thermic effect of feeding is acutely impacted by positive energy balance as an adaptive mechanism [7,8]. Activity thermogenesis, however, does appear to be a potential adaptive mechanism either cognitively through increased physical activity or involuntarily as seen in studies of overfeeding on nonexercise activity thermogenesis [9]. Another potential adaptation to times of positive energy balance could be in alterations in nutrient trafficking especially of fat with some individuals better able to mobilize fat, favoring oxidation [10]. Finally, those individuals who are resistant to weight gain may respond to periods of positive energy balance with subsequent reductions in energy intake. This could be in response to changes in physiologic modulators of appetite and/or due to changes in cognitive and/behavioral processes.

In work from our lab we have observed that thin (obese-resistant) individuals quickly sense changes in energy balance (short-term overfeeding) with significant changes in subjective measures of hunger and satiety [11]. By two meals these individuals have a significant

reduction in hunger ratings (Figure 1) and significant increases in satiety ratings. In addition, these individuals appear to also adapt by consuming less energy in the subsequent days. These findings are particularly true of the thin women. This is in contrast to reduced-obese (obese prone) individuals who do not appear to appropriately sense the changes in energy balance. It therefore appears that there is a regulation of ingestive behaviors which is altered by changes in energy balance, and that this regulation is more or less sensitive dependent on the phenotype. In other words, thin individuals appear to sense changes in energy balance more sensitively than obese prone individuals. The question that follows is what do we mean by “sensing” changes in energy balance? What is it about our response to energy balance that leads to changes in behaviors?

2. Regulation of Energy Balance

2.1 Homeostatic or Physiologic Regulation of Energy Intake

It is beyond the scope of this paper to review energy balance regulation in depth, and this topic has been previously reviewed [12-15]. The discovery of leptin has led to dramatic advances in the understanding of the homeostatic regulation of food intake. Adiposity signals, such as leptin and insulin, appear to negatively feedback to the hypothalamus to trigger signals ultimately resulting in reduced energy intake and increased energy expenditure. More recently gut peptides, such as ghrelin and PYY, have also been implicated in the regulation of energy intake again via hypothalamic signals. Furthermore, there appear to be interactions between the relatively acute gut signals with the more chronic adiposity signals.

2.2 “Non-Homeostatic” Regulation of Energy Intake

While a great deal has been learned about the homeostatic regulation of food intake and interactions with adiposity signals, it is clear, however, that the intake of food is a much more complex process that is not solely due to hypothalamic regulation. This is likely to be especially true in humans in which psychosocial factors play such a critical role and in which the process of eating is likely to be controlled by factors such as motivation, reward, and learned behaviors. As summarized in Table 1, ultimately the decision to initiate food intake, how much to consume, and when to terminate a meal is affected by not only these homeostatic mechanisms but also by learned behaviors, cognitive factors, habits, social context, availability of food, and external sensory cues such as visual, smell, and taste inputs [16].

It has been hypothesized that the regulation of food intake follows the structure of motivated behavior [17]. First, visceral and external sensory inputs are processed and integrated with reward and memory systems leading to an “incentive value” of the goal. Behavior is then initiated following the interaction of the internal state, such as state of energy balance, and the incentive value of the goal, i.e. food. This motivated ingestive behavior is the outcome of the integration of stimulatory, inhibitory, and disinhibitory neural circuits. Once the behavior has been initiated functions of reward and aversion, as well as, learning and memory are critical in this integrative process. As the behavior continues a number of feedback signals are at work leading to potential continuation versus termination of the behavior, feeding.

Reward systems are also powerful modulators of feeding behaviors. Most mammals will eat beyond their “needs” when presented foods that are highly palatable, and the rewarding effects of food in humans cannot be argued. Likely there is an interaction between the homeostatic mechanisms of feeding and the reward or hedonic effects [15,18]. For example, a food stimulus that may be pleasurable while hungry may lose its desirability when satiated [19]. This relates to the concept of “incentive” or “reinforcing” value of food. The hedonic preference for a food relates to the palatability or pleasantness of that food and is associated with the “liking” of food [20]. The incentive or reinforcing value of a food corresponds to the motivational value of that

food and the “wanting” of food [20]. The liking and wanting of food work together to effect the reinforcing value of food and ultimately the behavior, eating. Another interesting and related concept is that of Sensory-Specific-Satiety which relates to a reduction in response to a repetitive stimulus but not to a new stimulus.

In summary, the regulation of energy intake is a complex process. Interactions between homeostatic and non-homeostatic signals are likely critical for the ultimate regulation of energy intake (Figure 2).

3. Neuronal Response to Visual Food Cues

In order to further understand the potential adaptations to positive energy balance on food intake we initiated neuroimaging studies in individuals either resistant or prone to weight gain. We hypothesized that thin individuals, i.e. individuals who “adapt” effectively to periods of positive energy balance, would be sensitive to food-related visual stimuli and that the response to these stimuli would be attenuated in the overfed state when the internal milieu should promote reduced food intake. In contrast, we hypothesized that the neuronal response in reduced-obese individuals, i.e. individuals at high risk for weight gain, would not be affected by overfeeding. We hypothesized that food cues would, in fact, have greater incentive value in these weight-reduced individuals.

We used functional magnetic resonance imaging (fMRI) to examine the neuronal response to food-related visual cues. We chose food-related images as our stimulus because the sight of food is a key signal for the initiation of a meal; by seeing the food we are aware of its availability and potential palatability both of which impact the motivation to initiate food intake [21]. The sight and visual characteristics of food have been shown to have a significant impact on the incentive to eat in primates and have been shown to be associated with the activation of specific brain regions in humans [22-25]. Subjects were studied in the fasted state in a counter balance manner. On one occasion they were studied after two days of eucaloric diet, and on another occasion they were studied after two days of 30 percent overfeeding. Each group was examined alone and then in direct comparison.

3.1 Neuronal Responses in Obese-Resistant Individuals

We first examined the neuronal response to visual stimuli of foods of high hedonic value as compared to neutral foods or non-food objects in the baseline state in thin individuals [26]. Images of foods in general were associated with activation of insular cortex. Although usually considered the primary taste cortex, insula has also been shown to be a brain region important in the regulation of feeding behaviors [27-29] and may relate to the memory of the rewarding effects of food [30,31]. As shown in Figure 3A, images of foods of greater salience were associated with robust activation of bilateral inferior temporal visual cortices, premotor cortex, and hippocampus as well as (not shown) posterior parietal cortex, amygdala and hippocampus [26], all areas important in selective attention and reward [32]. Similar results in normal weight individuals have been shown by others [23-25]. It may be that when food is available and appears to be highly palatable and calorically dense, attention and motivation to eat is heightened. We also saw significant activation of the hypothalamus in response to these hedonic food visual cues. Although specific hypothalamic neurons or sub-regions cannot be ascertained, this suggests an important interaction between external sensory inputs and homeostatic signals [26]. This could also be interpreted as when desirable food is seen, i.e. when food is available and of high incentive value, the gain on the homeostatic or physiologic drive to eat is changed, promoting increased hunger and food intake.

Two days of positive energy balance, induced by 30% overfeeding, was associated with significant attenuation of the activation described in the eucaloric conditions [26]. Specifically,

Figure 3B shows that overfeeding was associated with not only attenuation of the activation of the visual and attention related brain regions but also with significantly reduced hypothalamic activity. In other words, these ‘obese-resistant’ individuals quickly and appropriately sense the positive energy balance associated with overfeeding, resulting in reduced attention for foods of high salience. In addition, reduced hypothalamus activation in response to overfeeding may reflect interactions between visual cues and the homeostatic status of the individual, i.e. in a state of positive energy balance the “gain” on the homeostatic regulation of energy balance is changed, potentially promoting a return to energy balance. It is unclear what changes in hypothalamic activation as measured by fMRI means exactly. The technique used is not sensitive enough to distinguish specific hypothalamic regions or neurons. Nevertheless, we believe that neural inputs to the hypothalamus in response to visual food stimuli are occurring via brain regions important in motivation and reward such as the nucleus accumbens, amygdala, insula and orbital frontal cortex.

3.2. Neuronal Responses in Obese-Prone Individuals

We then looked at the same conditions in reduced-obese individuals. Our preliminary findings showed that in the baseline state not only were visual and attention centers activated in response to visual food-related stimuli of high salience, as in thin individuals, but prefrontal cortex was also activated. This suggests that brain regions important in cognition and behavior planning are more likely to be activated in individuals prone to weight gain. Are they attempting to suppress these rewarding signals? Individuals with binge eating disorder and other “reduced-obese” models have also been shown to have increased prefrontal cortical activation in response to food exposure [33-35]. In addition, we saw less hypothalamic activation in obese-prone individuals, suggesting potentially altered interactions between homeostatic and nonhomeostatic signals.

Finally, positive energy balance was not sensed in the reduced-obese individuals in the same manner as in thin individuals. There was more persistent activation of visual cortex and attention centers in response to rewarding food images in these obese-prone individuals as if foods continue to appear interesting/rewarding despite overfeeding. In addition, we did not see reduced hypothalamic activation with overfeeding in this group, further suggesting impaired interactions between visual cues and homeostatic regulation of energy balance. Other investigators have found differences in the neuronal responses to a meal between obese and lean individuals [36-38].

3.2. Summary of Neuronal Responses

We found that brain regions associated with attention were activated in response to visual food cues of high salience. These “external” stimuli resulted in hypothalamic activation in the thin, obese-resistant phenotype. Food stimuli were more likely to activate cognitive and behavior-planning regions in the obese-prone phenotype. These responses were not only affected by the energy balance state but also the phenotype.

4. Concluding Remarks

As previously discussed, the regulation of energy intake is a complex process ultimately processed by the integration of internal and external sensory inputs. It has been hypothesized that the regulation of food intake follows the structure of motivated behavior [17]. First, visceral and external sensory inputs are processed and integrated with reward and memory systems leading to an “incentive value” of the goal. Behavior is then initiated following the interaction of the internal state, such as state of energy balance or hormonal changes, and the incentive value of the goal, i.e. food. This motivated ingestive behavior is the outcome of the integration of stimulatory and inhibitory neural circuits. Once food intake has been initiated, functions of

reward and aversion, as well as, learning and memory are critical in this integrative process. As food intake continues a number of feedback signals are at work leading to potential continuation versus termination of feeding [17]. Our findings are consistent with this concept. The metabolic state of the organism (eucaloric or overfeeding) impacts the incentive value of the “available” food. In a state of energy balance and after an overnight fast when individuals are “hungry” greater attention is placed toward food items of higher potential reward, i.e. a state of increased “wanting” for food. This is then associated with increased hypothalamic activation or activation of the homeostatic mechanisms associated with food intake. This could be interpreted as when we see food we turn on the signals that drive us to eat. In turn, when there is no food around, these signals are attenuated or when the organism does not need more food (overfeeding) these signals are attenuated or inhibited. We also find that these responses are altered in reduced-obese individuals, those at high risk for weight gain. It is unclear, however, whether this is a consequence of the weight loss or a reflection of pre-existing phenotypic differences.

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Figure 1. Mean pre-meal hunger ($\pm$ SEM) during eucaloric and overfeeding diet periods are shown. Overfeeding resulted in significant reductions in mean pre-meal hunger in the thin cohort [11].

Figure 2.
The integration of homeostatic and non-homeostatic signals in the regulation of energy intake.

Figure 3. The neuronal response to visual stimuli of foods of high hedonic value as compared to foods of neutral hedonic value in thin individuals in the (A) eucaloric state and (B) overfed state [26]. Mean BOLD responses ($\pm$ SEM) are shown for the hypothalamus in the eucaloric and overfed conditions and the visual cortex in the eucaloric state.

Figure 4.
The neuronal response to visual stimuli of foods of high hedonic value as compared to foods of neutral hedonic value in reduced-obese individuals in the eucaloric state.

Table 1

Non-homeostatic regulation of energy intake.

Internal Inputs	External Inputs
Reward Mechanisms	Environmental Cues:
“thinking” about food	- Sight
Cravings	- Smell
Learned Behaviors	- Taste
Attention	Availability
Habits	Social Context
	Habits