Exposure to appetitive food stimuli markedly activates the human brain

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Revised 22 September 2003; revised 18 November 2003; accepted 20 November 2003

Objective: The increased incidence of obesity most likely reflects changes in the environment that had made food more available and palatable. Here we assess the response of the human brain to the presentation of appetitive food stimuli during food presentation using PET and FDG. Method: Metabolic changes in response to food presentation were done in 12 healthy normal body weight subjects who were food deprived before the study. Results: Food presentation significantly increased metabolism in the whole brain (24%, P < 0.01) and these changes were largest in superior temporal, anterior insula, and orbitofrontal cortices. The changes in the right orbitofrontal cortex were the ones that correlated significantly with the increases in self-reports of hunger and desire for food. Discussion: The marked increase in brain metabolism by the presentation of food provides evidence of the high sensitivity of the human brain to food stimuli. This high sensitivity coupled with the ubiquitousness of food stimuli in the environment is likely to contribute to the epidemic of obesity. In particular, the activation of the right orbitofrontal cortex, a brain region involved with drive, may underlie the motivation to procure food which may be subjectively experienced as “desire for food” and “hunger” when exposed to food stimuli.

Keywords: PET; FDG; Food; Orbitofrontal cortex; Insula; Motivation

Introduction

The incidence of obesity in the United States and in the world has reached epidemic proportions and continues to rise (i.e., approximately 30% of adults in the United States are obese) (Flegal et al., 2002). The increased morbidity and mortality associated with obesity places a sense of urgency to understand the processes that have contributed to this epidemic. Of particular relevance is the environment, which has made food not only widely available but also increasingly more varied and palatable.

Although many signals that regulate food intake originate from internal sources that control caloric and nutrient intake (i.e., leptin, insulin, ghrelin, PYY), variables other than caloric intake and satiety have profound effects on food intake. These include the pleasurable sensory responses from food (i.e., palatability), emotional variables (i.e., stress, depression), and environmental factors (i.e., food availability, food related cues, alternative reinforcers) (Patel and Schlundt, 2001). Disruption in the sensitivity of the brain to these other variables could result in excessive eating and obesity. A particularly relevant variable is the sensory appeal and the conditioned responses that the food conveys to the subject. In a prior study with PET and [11C]raclopride, we showed that striatal dopamine release was associated with the desire for food during presentation of palatable food stimuli (Volkow et al., 2002a). This response was consistent with dopamine’s (DA) role in motivation for food (Martel and Fantino, 1996). However, DA's role is to regulate the activity of brain regions, which in turn are the ones that are likely to modulate the motivation for food consumption (nucleus accumbens, dorsal striatum, orbitofrontal cortex, and insula) (Bassareo et al., 2002; Chikama et al., 1997). Here we assessed the brain circuits activated by the presentation of food stimuli using the experimental paradigm that we had used to show DA increases in striatum with exposure to palatable food stimuli (Volkow et al., 2002a).

Methods

Twelve healthy right-handed subjects (seven female and five male subjects, age 28 ± 5 years old) were recruited for the study. Subjects with body mass index greater than 30 kg/m², history of eating disorders, surgical/medical treatment for weight control, dependence on alcohol or other drugs of abuse (except for caffeine <5 cups/day or nicotine <1 pack/day), neurological or psychiatric disorder, use of prescription (nonpsychiatric) medication(s) that can affect brain function in the past 2 weeks, medical conditions...
that may alter cerebral function, cardiovascular disease and diabetes, and head trauma with loss of consciousness of more than 30 min were excluded from the study. Urine screening tests for psychoactive drugs (including PCP, cocaine, amphetamine, opiates, barbiturates, benzodiazepine, and THC) were performed to corroborate lack of drug use. Written informed consents were obtained after the experimental procedure was explained and after the subjects had read the consent form. The protocol was approved by the Institutional Review Board at Brookhaven National Laboratory.

Subjects were scanned with 2-deoxy-2\[^{18}\text{F}\]fluoro-D-glucose (FDG) using a Siemens HR + positron emission tomography (PET) scanner. Details on procedures for positioning of the subjects, arterialized venous and venous catheterization, quantification of radiotracer, and transmission and emission scans have been published (Wang et al., 2003). Briefly, one emission scan (20 min) was taken 35 min after an intravenous injection of 4–6 mCi of FDG. During the study, subjects were positioned supine in the PET camera with their eyes open; the room was dimly lit and noise was kept to a minimum. Subjects were scanned twice with FDG in two different days under the following conditions. (1) Day A: Food presentation started 15 min before FDG injection and continued for a total of 45 min. (2) Day B: Neutral intervention started 15 min before FDG injection and continued for a total of 45 min. The sequence was randomized so that for half of the subject the first day was day A, while for the other half it was day B.

The subjects were asked to fill out a questionnaire, which contained the following information on the day of screening: a rating of the subject’s overall interest in food; what the subject’s favorite foods were; what food smells stimulated the subject’s appetite; what food smells diminished the subject’s appetite; and to rate a list of foods for their preferences on a scale from 1 to 10, 10 being the highest. The food items with the highest ratings were then selected to be presented to the subject during the food stimulation condition.

For the food stimulation condition, the subjects were asked to describe their favorite foods and how they like to eat them while they were presented with foods that they had reported as among their favorite ones. The food was warmed to enhance the smell and the subjects were presented with it so that they could view it and smell it. A cotton swab impregnated with the food was placed in their tongues so they could taste it. A given food item was presented for 5 min and then it was exchanged for a new one. For the neutral intervention, subjects were asked to describe in as much detail as possible their family genealogy while they were presented with nonfood related items (paper photographs of nature scenes, of humans, and of animals), which they were allowed to smell, and a cotton swab impregnated with water was placed in their tongues and lips as was done for the food condition. The food and the neutral interventions were started 15 min before radiotracer injection and were continued for a total of 45 min. Subjects were asked to have their last meal at 7 PM the evening before the day of the study and were studied between 17 and 19 h after the last meal.

During the PET studies, participants were instructed to orally respond to each descriptor using a whole number between 1 and 10 for the self-report of “hunger” and “desire of food”, which were obtained before the food presentation and then at 5-min intervals for a total of 45 min.

Regions of interest (ROI) in orbitofrontal cortex, anterior insula, parietal cortex, temporal cortex, caudate, putamen, and thalamus were obtained using a template, which we had previously published (Wang et al., 2003). We also computed a value for global metabolism by averaging the activity in the 63 planes scanned. To minimize the effects of overall changes in brain metabolism on the regional measures, we normalized them using the ratio of the region to the global metabolic measures (“relative” measures).

Fig. 1. Transaxial FDG-PET brain images of a subject during food presentation and during neutral intervention at levels of postcentral gyrus, superior temporal cortex, insula, and orbitofrontal cortex. The metabolic images for both scans are scaled with respect to the maximum absolute metabolic value obtained on the neutral intervention and presented using the rainbow scale, where red represents the highest value and dark violet represents the lowest value.
Differences in metabolism between the measures obtained in the food presentation and neutral intervention conditions were tested with paired samples \( t \) tests. Pearson product moment correlations were used to assess the relationship between the changes in metabolism and the changes in the behavioral measures between the food and neutral interventions.

Differences in metabolism between the two conditions were also tested on the voxel level using the software package for Statistical Parametric Mapping (SPM99 Software, 1999). Before the analysis, each subject's PET image was mapped onto the Montreal Neurological Institute template, which closely resembles the Talairach brain and smoothed via a Gaussian kernel with full width half maximum (FWHM) at 16 mm. The relative (normalized) metabolic image was obtained by dividing the signal level of each voxel with the global mean, which is the average signal level of all voxels in the PET image. The analysis, which was essentially a paired samples \( t \) test performed on each voxel, was performed using both the absolute and the relative metabolic images. Multiple-test correction was performed via the random field theory less conservative than the traditional approach such as the Bonferroni method (Worsley et al, 1996). Pixels that were significantly different from those in the neutral presentation \( (P < 0.05) \) were identified with respect to the Talairach and Tournoux stereotactic coordinates (Talairach and Tournoux, 1988) and displayed on the axial MR images. The threshold for the cluster size was set at 100 voxels. Only regions with corrected \( P \) values \( < 0.05 \) at the cluster level were considered significantly activated or deactivated.

**Results**

The body weight of the subjects was between 110 and 210 lb (average: 147.5 ± 32.4 lb). The averaged body mass index of the

![Graph showing changes in metabolism between food presentation and neutral intervention conditions.](image-url)
subjects was 24 ± 2.6 (range: 20–29). The favorite food items most frequently selected by the subjects were bacon–egg–cheese sandwich, cinnamon bun, pizza, hamburger with cheese, fried chicken, lasagna, Bar-Be-Que rib, ice cream, brownie, and chocolate cake.

Compared to the neutral intervention condition (36 ± 2 μmol/100g/min), the food presentation (45 ± 9 μmol 100 g⁻¹ min⁻¹, \( P < 0.01 \)) significantly increased whole brain metabolism (+24 ± 21%). The absolute regional metabolic measures were also significantly higher for all brain regions (except in the occipital cortex) for the food than the neutral condition (Figs. 1 and 2). Normalization by whole brain metabolism (relative metabolic measures) revealed that (Fig. 3) the largest increases were in the left and right postcentral gyrus (left: +14.9 ± 11.6%, \( P < 0.0001 \); right: +8.5 ± 7.9%, \( P < 0.012 \)), left superior temporal (+11.2 ± 9.2%, \( P < 0.002 \)), left anterior insula (+9.6 ± 14.6%, \( P < 0.03 \)), and left orbitofrontal cortex (+8.9 ± 12.3%, \( P < 0.015 \)).

The SPM analyses of the absolute metabolic values at a significance level of \( P < 0.0001 \) (voxel level) showed a large contiguous cluster (72,865 voxels) in bilateral cortical (inferior frontal, parietal, temporal, occipital, and cerebellar regions) and subcortical structures with food presentation. The results from SPM with the relative metabolic measures (Fig. 4) corroborated the findings obtained using the ROI method. The SPM analyses yielded a large contiguous cluster (8339 voxels) in the left parietotemporal cortices and two smaller clusters: one in the right parietotemporal cortex (1679 voxels) and one in the left orbitofrontal cortex (499 voxels) with food presentation. The large cluster in the left parietotemporal cortices encompassed three subclusters that included the posterior central gyrus (Brodmann’s areas 1): (−42,−26, 30); the left insula: (−44,−6, 2); and the left superior temporal gyrus: (−60,−30,−2). The significance of this cluster was \( P < 0.004 \) (corrected at the cluster level). The significance for the cluster in the right parietotemporal cortex (62,−16, 20) was \( P < 0.05 \) (uncorrected at the cluster level). The cluster in the left orbitofrontal cortex was not significant at the cluster level; however, there were two voxel-level significant regions (−38, 44, 4, \( P < 0.01 \); −38, 56, 2, \( P < 0.02 \)).

Fig. 3. Relative brain metabolic changes between food presentation and neutral intervention conditions. A, \( P < 0.005 \); B, \( P < 0.05 \).
Fig. 4. SPM images showing the areas with higher metabolism in food presentation than in neutral intervention condition. Color-coded SPM results displayed in a transaxial plane with a superimposed with brain MR images (grayscale). The results ($T$ value) are presented using the color scale, where white represents the high value and red represents the low value. SS: somatosensory cortex; In: insula; ST; superior temporal cortex; OF: orbitofrontal cortex.

Fig. 5. Time sequence of self-report ratings of hunger and desire for food during food presentation condition. The subjects reported increases in the ratings of hunger (+25%) and desire for food (+28%) as compared to the baseline (0 min).

Fig. 6. Correlation between changes in right orbitofrontal metabolism and self-report rating of hunger was significant ($r = 0.84$, $P = 0.001$).
The food presentation condition resulted in significant increases in the ratings of hunger (25 ± 26%, $P = 0.006$) and desire for food (28 ± 27%, $P = 0.007$, Fig. 5). The correlation analyses showed a significant association between relative metabolic changes in the right orbitofrontal cortex and the self-reports of hunger ($r = 0.84$, $P = 0.001$, Fig. 6) and desire for food ($r = 0.77$, $P = 0.006$). No significant correlations were found between the behavioral measures and the metabolic changes in the insula, postcentral gyrus, and superior temporal regions.

**Discussion**

This study shows that presentation of food stimuli to fasting subjects resulted in marked increases in whole brain metabolism (24%). The increases in metabolism were largest in left cortical regions (postcentral gyrus, superior temporal cortex, insula, and orbitofrontal cortex). There is no conclusive evidence regarding a lateralized representation for processing of chemosensory stimuli in the brain. Indeed, some studies have reported right hemisphere dominance (Small et al., 1999), while others reported bilateral (Faurion et al., 1999) or left hemispheric (Del Parigi et al., 2002) activation in response to chemosensory stimulation. In our study, the predominant activation in the left hemisphere could reflect the experimental conditions used for the food and the neutral stimulations.

Food stimulation resulted in activation of the postcentral region on the lateral surface of the parietal cortex, which is where the somatosensory map of the tongue is located and is an area involved with taste perception (Heimer, 1995). Thus, its activation is consistent with its known role in the somatosensory perception of food. The reward associated with the taste of food (influenced by palatability) is distinctively different from that associated with food ingestion (influenced by hunger/satiety). Palatability increases food intake through a positive-feedback reward mechanism that involves opioid and GABA/benzodiazepine systems (Cooper, 1989; Yeo-mans and Gray, 2002). We had previously observed during non-stimulation conditions (resting state) enhanced brain activity in this somatosensory region in morbidly obese subjects when compared to normal-weight subjects (Wang et al., 2002). This led us to postulate that enhanced activity in this region could make an individual more sensitive to the rewarding properties of food related to palatability and could be one of the variables contributing to excess food consumption. Similarly, in obese women, cerebral blood flow in parietal cortex was found to be significantly higher than in normal-weight subjects (Karhunen et al., 1997).

The anterior insula showed activation during the food presentation, which is consistent with its role as a primary gustatory cortex (O’Doherty et al., 2001; Yaxley et al., 1990; Zald et al., 1998). The activation of the insula has been observed with fasting (Morris and Dolan, 2001; Tataranni et al., 1999) and during activation with unpleasant and aversive food-eating conditions (O’Doherty et al., 2001; Zald et al., 1998). The anterior insular region has also been implicated in the processing of visceral sensations (Allen et al., 1991; Small et al., 1999). Indeed, insular activation has been reported during temperature and pain perception (Casey et al., 1996).

The OFC has been identified as a secondary gustatory cortex (Rolls et al., 1990). It is believed that the OFC is involved with the rapid learning of visual, olfactory, and taste associations (Rolls, 1997). The OFC receives projections from the insula, striatum, and amygdala. These connections place the OFC in a position to process information about the motivational value of gustatory stimuli. Neurons in the OFC are modulated by the motivational state of the animal, which respond to the sight or taste of food when the animal is hungry but do not respond when the animal is satiated (Rolls, 1989). The neurons in the OFC respond selectively to rewards or aversive stimuli and process the relative preference for food rewards (Tremblay and Schultz, 1999). The OFC is also involved in processing tastes that have both positive and negative affective valence (O’Doherty et al., 2001). Primate studies have shown not only taste but also smell-responsive cells throughout the posterior OFC (Rolls et al., 1999). The present study showed increased metabolic activity in the left posterior OFC in response to the food presentation, which included tasting and smelling of food. Thus, its activation, which was not associated with the subjective perception of hunger or desire of food, is likely to reflect its involvement in processing the valence of the flavors and of the smells from the stimuli. In contrast, the right OFC was significantly associated with the perception of hunger and desire for food. A similar correlation had previously been reported by a PET study that showed a positive correlation between increases in cerebral blood flow in right posterior OFC and hunger ratings during presentation of food items (Morris and Dolan, 2001). This association is consistent with the known role of the OFC in processing expectation of food reward (Watababe, 1996). Wanting food (or appetite) is modulated by DA pathways in part by modulating activity in the OFC (Berridge, 1996; Spanagel and Weiss, 1999). Indeed, imaging studies have shown that metabolic activity in the OFC is in part regulated by DA activity (Volkow et al., 1993, 2002b).

Using the same food-stimulation paradigm, we previously showed DA increases in the striatum during food stimulation that were also associated with the “desire for food” and with the perception of “hunger” (Volkow et al., 2002b). Thus, the current studies suggest that the enhanced OFC activation by the food stimulation may reflect downstream effects from DA stimulation and that DA’s involvement in the drive for food consumption in human subjects is in part mediated by its effects in the OFC. The results could explain the deleterious effects of constant exposure to food stimuli (e.g., advertisements, candy machines, food channels, stores) in overeating (Coon and Tucker, 2002). It also raises the possibility that being a food management professional (e.g., chef) may pose a risk for overeating particularly in those at higher genetic risk for obesity similar to the higher risk for drug abuse and addiction in anesthesiologists who as part of their work are constantly exposed to psychoactive drugs with abuse potential (Tirrell, 1994). In nonhuman primates, lesions of the OFC produce abnormal eating behavior (Baylis and Gaffan, 1991). The OFC is a brain region that has been implicated in the compulsive behaviors characteristic of drug addictive states (Volkow and Fowler 2000). Indeed, activation of the right OFC cortex was shown to be associated with cocaine craving induced by stimulant administration in cocaine-addicted subjects (Volkow et al. 1999). Markedly increased metabolic activity in the OFC was also reported during cue-induced cocaine craving in drug-addicted subjects (Bonson et al., 2002; Grant et al., 1996; Wang et al., 1999). This suggests that the same brain region, which is linked with the desire for natural stimuli (food), is also linked with drug craving in drug-addicted subjects. Thus, disrupted OFC activity could also possibly underlie the compulsiveness and lack of control in the eating behaviors of morbidly obese subjects.
Although no studies have demonstrated abnormalities in the OFC in obese subjects, we have reported decreases in DA D2 receptors in obese individuals (Wang et al., 2001). Since our previous studies in drug-addicted subjects showed an association between decreases in DA D2 receptors and metabolism in OFC (Volkow et al., 1993, 2001), further studies are warranted to assess if indeed there are abnormalities in the OFC in obese subjects.

Conclusion

The marked activation of brain metabolism by the presentation of food provides evidence of the high sensitivity of the human brain to the presence of food stimuli. This high sensitivity coupled with the ubiquitousness of food stimuli in the environment is likely to contribute to the epidemic of obesity. In particular, the activation in the right orbitofrontal cortex, a brain region involved with drive, may underlie the motivation to procure food, which may be subjectively experienced as “desire for food” and “hunger”.

Acknowledgments

This research was carried out at Brookhaven National Laboratory (BNL) under support by the U.S. Department of Energy OBER (DE-AC02-76CH00016) and by the National Institute on Drug Abuse (DA 7092-01 and DA00280). We thank David Schlyer and Michael Schueler for Cyclotron operations; Donald Warner and David Alexoff for PET operations; Richard Ferrieri, Colleen Shea, Youwen Xu, Victor Garza, and Payton King for radiotracer preparation and analysis; Karen Apelskog for study protocol preparation; and Noellwah Netusil, Pauline Carter, and Naomi Pappas for patient care and recruitment.

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