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"Nonhedonic" Food Motivation in Humans Involves Dopamine in the Dorsal Striatum and Methylphenidate Amplifies This Effect

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ABSTRACT The drive for food is one of the most powerful of human and animal behaviors. Dopamine, a neurotransmitter involved with motivation and reward, its believed to regulate food intake in laboratory animals by modulating its rewarding effects through the nucleus accumbens (NA). Here we assess the involvement of dopamine in "nonhedonic" food motivation in humans. Changes in extracellular dopamine in striatum in response to nonhedonic food stimulation (display of food without consumption) were evaluated in 10 food-deprived subjects (16–20 h) using positron emission tomography (PET) and [^{11}C]raclopride (a D2 receptor radioligand that competes with endogenous dopamine for binding to the receptor). To amplify the dopamine changes we pretreated subjects with methylphenidate (20 mg p.o.), a drug that blocks dopamine transporters (mechanism for removal of extracellular dopamine). Although the food stimulation when preceded by placebo did not increase dopamine or the desire for food, the food stimulation when preceded by methylphenidate (20 mg p.o.) did. The increases in extracellular dopamine were significant in dorsal ($P < 0.005$) but not in ventral striatum (area that included NA) and were significantly correlated with the increases in self-reports of hunger and desire for food ($P < 0.01$). These results provide the first evidence that dopamine in the dorsal striatum is involved in food motivation in humans that is distinct from its role in regulating reward through the NA. In addition it demonstrates the ability of methylphenidate to amplify weak dopamine signals. **Synapse 44:175–180, 2002.**

INTRODUCTION

The drive for food is one of the most powerful of human and animal behaviors. Food intake is regulated by multiple factors, including caloric requirements as well as the reinforcing responses to food (Smith, 2000). Dopamine (DA) is one of the neurotransmitters involved in regulating food consumption through modulation of the rewarding properties of food (Martel and Fantino, 1996). Microdialysis and electrochemical studies in laboratory animals have shown increases in striatal extracellular DA both during food expectation (Mark et al., 1994; Kiyatkin and Gratton, 1994) and food consumption (Bassareo and Di Chiara, 1997; Taber et al., 1997). Moreover, injection of DA into the nucleus accumbens (NA), which is the nucleus in the striatum associated with reinforced behaviors (Berridge, 1996; Bassareo and Di Chiara, 1999), can stimulate feeding (Swanson et al., 1997) and depletion of DA in striatum abolishes ingestive behaviors (Ungerstedt, 1971; Zhou and Palmiter, 1995). DA-deficient mice (tyrosine-hydroxylase gene knockout) are hypophagic and die of starvation unless DA activity is restored in the striatum (Szczypka et al., 2001). The role of brain DA in food consumption in humans has been much less investigated. Using positron emission tomography (PET), we showed that pathologically obese subjects have reductions in striatal DA D2 and showed an inverse association between body mass index (BMI) and DA D2 receptors (Wang et al., 2000). We inter-

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preted these findings as evidence of the role of the DA system in regulating food intake in obese subjects.

Here we extend these studies to investigate the role of DA in food intake in healthy nonobese subjects. We hypothesize that food-related stimuli would increase extracellular DA in striatum in proportion to their ability to increase hunger and desire for food. For this purpose, 10 healthy male subjects were studied with PET and [^{11}C]raclopride, a DA D2 receptor ligand sensitive to competition with endogenous DA (Seeman et al., 1996; Volkow et al., 1994). Food-deprived subjects were studied while stimulated with a neutral or with a food-related stimulus. To amplify the DA changes we pretreated subjects with methylphenidate, a drug that blocks dopamine transporters (Volkow et al., 1998) (mechanism for removal of extracellular dopamine; Giros et al. [1996]). To control for the effects of methylphenidate on extracellular DA we also studied the effects of methylphenidate after a neutral stimulus. Because [^{11}C]raclopride binding is highly reproducible (Volkow et al., 1993) differences in binding between placebo and the intervention predominantly reflect intervention-induced changes in extracellular DA (Dewey et al., 1993; Breier et al., 1997).

MATERIALS AND METHODS

Subjects

Ten healthy controls (eight males, two females; 35 ± 8 years of age) were studied. Written informed consent was obtained in all subjects after a complete description of the study and following the guidelines set by the Institutional Review Board at Brookhaven National Laboratory.

Scans

PET studies were carried out with an HR+ tomograph (resolution 4.5 × 4.5 × 4.5 mm full width half-maximum, 63 slices) using [^{11}C]raclopride as a DA D2 receptor ligand (Volkow et al., 1993). Methods for positioning of subjects, catetherizations, transmission scans, and blood sampling and analysis have been published (Volkow et al., 1993). Briefly, emission scans were started immediately after injection of 4–8 mCi (specific activity 0.5–1.5 Ci/μM at EOB). A series of 20 emission scans were obtained from time of injection up to 54 min. Arterial sampling was used to quantitate total carbon-11 and unchanged [^{11}C]raclopride in plasma.

Subjects were scanned four times with [^{11}C]raclopride under the following four conditions: 1) neutral stimulation preceded by oral placebo ($neutral_{placebo}$); 2) neutral stimulation preceded by oral MP ($neutral_{MP}$); 3) food stimulation preceded by oral placebo ($food_{placebo}$); and 4) food stimulation preceded by MP ($food_{MP}$). Subjects were scanned over a 2-day period, the order of which was randomly varied. On one day the first scan was the $neutral_{placebo}$ and the second, which was done 2 h later, was the $food_{MP}$. For the other day the first scan was the $food_{placebo}$ and the second, which was done 2 h later, was the $neutral_{MP}$. The placebo (calcium carbonate) or the MP (20 mg) were given 45 min prior to the food and neutral stimulations, which were started 15 min prior to the injection of [^{11}C]raclopride. Venous blood was drawn for quantification of plasma concentrations of the two enantiomers of MP (D-threo and L-threo methylphenidate) prior to and at 1, 2 and 3 h after oral MP using capillary GC/mass spectrometry (Srinivas et al., 1991).

Stimulation

For the food stimulation experiments, the subjects were presented with foods that they had previously reported as among their favorites. The food was warmed to enhance the smell and the subjects were presented with it so that they could view it and smell it and a cotton swab impregnated with the food was placed on their tongues so they could taste it. A given food item was presented for 4 min and then it was exchanged for a new one. For the neutral stimulation, subjects were asked to describe in as much detail as possible their family genealogy. The food and the neutral stimulations were started 15 min prior to radiotracer injection and were continued for a total of 40 min. Subjects were asked to have their last meal at 7 PM the evening before the day of the study and were studied between 16–20 h after the last meal.

Behavioral measures

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 prior to the food stimulation and then at 5-min intervals for a total of 40 min. In addition, self-reports of "alertness," "friendliness," "stimulation," and "talkativeness" were obtained prior to placebo and prior to the behavioral stimulation as previously described (Wang et al., 1997). Heart rate and blood pressure were monitored continuously.

Image analysis

Regions of interest (ROIs) were outlined for striatum (ST) and cerebellum (CB), as described previously (Volkow et al., 1993). Briefly, ROIs were initially outlined on the individual's summed baseline [^{11}C]raclopride image (images obtained between 15–54 min) and were then projected into the dynamic [^{11}C]raclopride images to generate time–activity curves for ST (dorsal and ventral) and CB. These time–activity curves for tissue concentration, along with the time–activity curves for unchanged tracer in plasma were used to calculate [^{11}C]raclopride's transfer constant from plasma to brain (K1) and the distribution volume (DV), which corresponds to the equilibrium measurement of

the ratio of tissue concentration to plasma concentration, in ST and CB using a graphical analysis technique for reversible systems (Logan et al., 1990). The ratio of DV in ST to that of DV in CB corresponds to (B_{max}/K_d) +1 and is insensitive to changes in cerebral blood flow (Logan et al., 1994). The response to food stimulation (with placebo or with MP) was quantified as the difference in B_{max}/K_d with respect to the $neutral_{placebo}$ condition, which was the condition used as baseline. Similarly, the response to MP with the neutral stimulation (used as a measure of MP's effects) was quantified as the difference in B_{max}/Kd with the $neutral_{placebo}$ condition.

Data analysis

Differences in B_{max}/K_d between conditions were tested using repeated ANOVA and post-hoc *t*-tests were then used to determine for which conditions the effects differed from the baseline condition ($neutral_{placebo}$). The effects of the food stimulation on the behavioral self-reports were tested by comparing the scores obtained prior to stimulation and the averaged scores obtained between 15–40 min after initiation of the intervention using repeated ANOVA. Pearson product moment correlations were used to assess the relationship between the food stimulation-induced changes in B_{max}/K_d and the behavioral effects of the food stimulation. Correlations were also performed between the changes in DA induced by MP when given with the neutral stimulation vs. the changes when given with the food stimulation.

RESULTS

The distribution volume images for one of the subjects for the four testing conditions: $neutral_{placebo}$ (condition used as baseline), $food_{placebo}$ (condition used to assess the effects of the food stimuli by itself), $neutral_{MP}$ (condition used to assess the effects of MP by itself), and $food_{MP}$ (condition used to assess the effects of the food stimuli when amplified by preblockade of the DA transporters with MP) are shown in Figure 1. The repeated ANOVA showed significant differences across the conditions for DA D2 receptor availability (B_{max}/K_d) in dorsal striatum ($F = 3.3$, df 3,27, $P < 0.05$) but not in ventral striatum (Table I). Post-hoc *t*-tests showed that when compared with the baseline condition the B_{max}/K_d measures in dorsal striatum were significantly lower for the $food_{MP}$ ($10 \pm 7\%$; $P < 0.005$) and the $neutral_{MP}$ conditions ($5 \pm 6\%$; $P < 0.05$). The $food_{MP}$ condition also tended to be lower than the $food_{placebo}$ condition and the $neutral_{MP}$ condition, but these differences were not significant. The $food_{placebo}$ condition did not differ from the $neutral_{placebo}$ condition, indicating that the food stimulation by itself did not induce a large enough change in extracellular DA to be resolved by the [^{11}C]raclopride method.

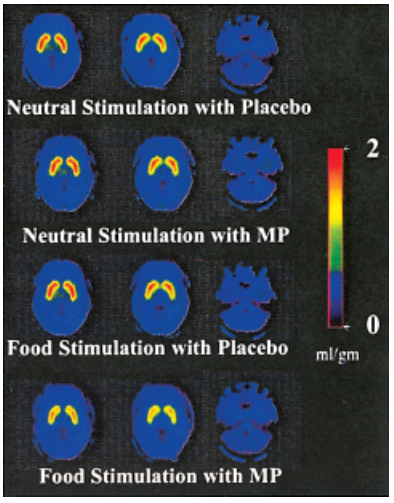

Fig. 1. Distribution volume images of [^{11}C]raclopride at the level of the striatum and at the level of the cerebellum for one of the subjects for the four scanning conditions: neutral stimulation with placebo, neutral stimulation with methylphenidate (MP), food stimulation with placebo, and food stimulation with MP. Binding of [^{11}C]raclopride in the striatum was lowest during food stimulation with MP.

TABLE I. Group average measures of B_{max}/K_d for the dorsal and the ventral striatum for the four testing conditions

	Dorsal striatum	Ventral striatum
$Neutral_{placebo}$	3.27 ± 0.34	2.67 ± 0.68
$Neutral_{MP}$	3.08 ± 0.33*	2.49 ± 0.56
$Food_{placebo}$	3.13 ± 0.32	2.47 ± 0.62
$Food_{MP}$	2.92 ± 0.27**	2.51 ± 0.35

Comparisons are with respect to $neutral_{placebo}$, which was the condition used as baseline. *$P < 0.05$, **$P < 0.005$.

TABLE II. Self-reports for "hunger" and "desire for food" before and after food stimulation when it was preceded by placebo ($Food_{placebo}$) and when it was preceded by MP ($Food_{MP}$)

	Prestimulation	Poststimulation
Hunger		
$Food_{placebo}$	8.1 ± 3	8.5 ± 3
$Food_{MP}$	6.0 ± 3	9.2 ± 1*
Desire for food		
$Food_{placebo}$	8.0 ± 3	8.5 ± 3
$Food_{MP}$	6.0 ± 3	9.4 ± 1*

*Comparisons correspond to repeated ANOVA $P < 0.005$.

Analysis of the behavioral measures showed a significant effect of the food stimulation condition on the self-reports of "hunger" and "desire of food" when it was preceded by MP ($P < 0.005$) but not when it was preceded by placebo (Table II). The differences in the other behavioral measures did not differ across conditions (data not shown).

The correlation analyses showed a significant association between the changes in extracellular DA and the self-reports of "hunger" and "desire for food" ($r = 0.76$, $P < 0.01$) when the food stimulation was given with MP (Fig. 2A). Although the correlation between the changes in extracellular DA and the self-reports of "hunger" when given with placebo was also significant

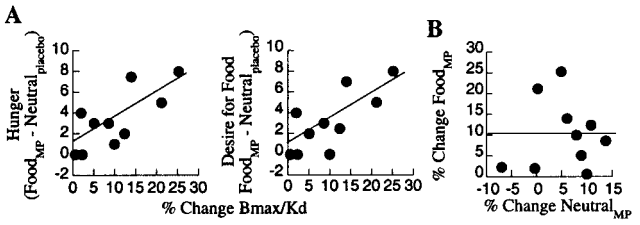

Fig. 2. **A**: Relationship between changes in B_{max}/K_d and the changes in self-reports of "hunger" and "desire for food" for the food stimulation with MP condition ($food_{MP}$; r = 0.76, $P < 0.01$). **B**: Relationship between changes in extracellular DA in dorsal striatum induced by MP when given with the neutral stimulation ($neutral_{MP}$) vs. the changes when given with the food stimulation ($food_{MP}$). This relationship was not significant (r = 0.03, $P = 0.93$).

(r = 0.64, $P < 0.05$), this was mostly driven by one datapoint.

To assess the extent to which the DA increases with $food_{MP}$ reflected the changes induced by food stimulation rather that MP's isolated effects, we examined the correlation between the changes in DA induced by MP for $neutral_{MP}$ vs. $food_{MP}$. This correlation was not significant (r = 0.03, $P = 0.93$) (Fig. 2B), indicating that the changes in DA reflect primarily the stimulation conditions under which MP was given.

The plasma MP concentrations were the same in the $neutral_{MP}$ and the $food_{MP}$ conditions (8 ± 7 and 7 ± 7 ng/ml, respectively, at 60 min). The DA changes were not correlated with the plasma MP concentration either for the $neutral_{MP}$ (r = 0.44, $P = 0.23$) or for the $food_{MP}$ conditions (r = 0.11, $P = 0.78$), indicating that differences in MP metabolism were not responsible for the changes in [^{11}C]raclopride binding.

DISCUSSION

This study shows that food stimulation in combination with oral MP elicits a significant increase in extracellular DA in the dorsal striatum. It also shows a correlation between the increases in DA induced by the food stimulation in combination with MP and the changes in the self-reports of "hunger" and "desire for food," which suggests that the DA increases during the $food_{MP}$ condition reflect the responses to food stimulation and not the isolated effects of MP. This association provides evidence that the DA system in the dorsal striatum plays a role in food motivation in the human brain. Surprisingly, such a relationship was not observed for the ventral striatum, which includes the NA, since this is the area traditionally implicated in motivation for food (Hernandez and Hoebel, 1988; Phillips et al., 1993; Richardson and Gratton, 1996; Bassareo and Di Chiara, 1999). However, a recent study showed that DA-deficient mice (tyrosine-hydroxylase gene knockout) die of starvation unless DA activity was restored in dorsal striatum, while rescuing DA in the NA restored their ability to choose between a palatable and a nonpalatable solution but was insufficient for survival (Szczypka et al., 2001). Thus, at least two roles of DA are involved in regulating food intake; one in dorsal striatum that maintains caloric requirements for survival, and one in NA involved in the rewarding properties of food. Our data are consistent with this view; since food was not consumed there was no reward and the ventral striatum was not activated. However, we cannot completely rule out the possibility that some degree of DA increase did occur in the NA but that the limited spatial resolution of the PET scanner interfered with our ability to detect it (Bendriem et al., 1991).

In this study, the effects of food stimulation by itself were insufficient to elicit a measurable response with the [^{11}C]raclopride method. This most likely reflects our methodology's limited sensitivity for detection of the modest DA changes expected with food stimuli (Hernandez and Hoebel, 1988). It was predicted that MP, by blocking DA's removal from the extracellular space, would amplify the DA changes due to food stimulation and enhance detection with [^{11}C]raclopride. However, since MP by itself also increased extracellular DA, it was important to rule out that the increases induced by the food stimulation when preceded by MP reflected the changes induced by the food stimulation rather than MP's isolated effects. The fact that there was a complete lack of an association between the changes on DA induced by MP when given with the neutral vs. when given with the food stimulation (Fig. 2B) provided evidence that MP's effects were driven by the conditions at which it was being given. The effects of the food stimulation on "hunger" and "desire for food" and on the increases in extracellular DA were only significant when they were preceded by MP, which supports our hypothesis that MP amplified the effects of the food stimulation condition. Thus, the use of low doses of oral MP could be applied to amplify DA signals elicited by behavioral stimuli that induce DA signals that are not large enough to be detected by the [^{11}C]raclopride PET method. Although two studies have shown decreased [^{11}C]raclopride binding with behavioral interventions—one after a video game with monetary reward (Koepp et al., 1998) and another after a placebo intervention in patients with Parkinson's disease (de la Fuente-Hernandez et al., 2001)—one study did not show an effect after exercise (Wang et al., 2000). These differences most likely reflect the magnitude of the DA changes elicited by the various behavioral interventions. Also, in the case of the placebo study (de la Fuente-Hernandez et al., 2001) it is possible that the low levels of DA transporters in the Parkinson's disease patients may have amplified the DA signals elicited by the expectation of a therapeutic effect.

Increases in hunger elicited by food stimulation plus MP were unexpected, since a frequent side effect of MP is anorexia (Golinko, 1984; Efron et al., 1997). This seeming paradox may reflect our experimental design,

where food-deprived subjects were exposed to food-conditioned stimuli but could not eat. In fact, preclinical studies have shown that stimulant drugs enhance the incentive salience of food-conditioned stimuli (Wyvell and Berridge, 2001; Files et al., 1989) and can increase food consumption (Konopacki et al., 1985). These experiments in laboratory animals as well as the present data are consistent with the notion that DA increases the incentive salience of a conditioned cue (e.g., the sight, smell, and taste of food), causing the cue to increase the motivational state of "wanting" for the reward without necessarily enhancing its hedonic properties (Richardson and Gratton, 1996; Berridge and Robinson, 1998).

The following are study limitations: 1) Although changes in [^{11}C]raclopride binding are linearly related to extracellular DA in animal experiments (Breier et al., 1997), the precise relationship with synaptic DA is not understood (Laruelle et al., 1997). 2) To avoid the need for four arterial cannulations in each subject, we conducted the studies over 2 rather than 4 days. This required that we always give MP during the second study of the day. However, it is unlikely that 2 extra hours of food deprivation (out of 16–20) would have changed the effectiveness of the food stimulation condition. Also, the order effect cannot explain the differences observed with MP when given with neutral vs. food stimulation. 3) The food stimulation condition involved multiple sensory modalities, whereas the neutral condition did not. However, this is unlikely to have affected the findings since there were no differences between the neutral$_{placebo}$ and the food$_{placebo}$ conditions.

These results provide the first evidence of the involvement of DA neurotransmission in dorsal striatum in mediating food motivation in the human brain. The dorsal striatum may be involved in "nonhedonic" variables that modulate food motivation, since DA increases were observed with food-conditioned stimuli presented without food consumption. These findings identify a role for DA in food motivation in humans that is distinct from its role in regulating food's rewarding effects through the NA.

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