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Sweet Dopamine: Sucrose Preferences Relate Differentially to Striatal D_2 Receptor Binding and Age in Obesity

Alterations in dopaminergic circuitry play a critical role in food reward and may contribute to susceptibility to obesity. Ingestion of sweets releases dopamine in striatum, and both sweet preferences and striatal D_2 receptors (D2R) decline with age and may be altered in obesity. Understanding the relationships between these variables and the impact of obesity on these relationships may reveal insight into the neurobiological basis of sweet preferences. We evaluated sucrose preferences, perception of sweetness intensity, and striatal D2R binding potential (D2R BP_{ND}) using positron emission tomography with a D2R-selective radioligand insensitive to endogenous dopamine, (N-[^{11}C] methyl)benperidol, in 20 subjects without obesity (BMI 22.5 ± 2.4 kg/m^2; age 28.3 ± 5.4 years) and 24 subjects with obesity (BMI 40.3 ± 5.0 kg/m^2; age 31.2 ± 6.3 years). The groups had similar sucrose preferences, sweetness intensity perception, striatal D2R BP_{ND}, and age-related D2R BP_{ND} declines. However, both striatal D2R BP_{ND} and age correlated with sucrose preferences in subjects without obesity, explaining 52% of their variance in sucrose preference. In contrast, these associations were absent in the obese group. In conclusion, the age-related decline in D2R was not linked to the age-related decline in sweetness preferences, suggesting that other, as-yet-unknown mechanisms play a role and that these mechanisms are disrupted in obesity.

Obesity is caused by ingesting more energy than expended over a long period of time. However, the mechanisms involved in regulating food intake are complex and not completely understood. A growing body of evidence suggests that neural circuits involved in reward and motivation pathways, typically studied in the context of addiction, interact with classic homeostatic regulatory brain areas to cause hedonic hyperphagia and contribute to the development of obesity (1). Data from several studies that involved blood oxygen level–dependent (BOLD) functional MRI have shown that food consumption elicits a smaller BOLD response in the dorsal striatum in subjects with obesity than those who are lean (2,3), presumably mediated by reduced striatal dopaminergic functioning.

The dopamine system plays a critical role in mediating the rewarding effects of food ingestion and thereby influences ingestive behavior. For example, dopamine-deficient rodents stop eating and die of starvation, but these animals can be rescued by restoring dopamine signaling either systemically (4) or within the dorsal, but not ventral, striatum (5). The evolutionarily conserved organization of the striatum serves, in part, to differentially encode and regulate the hedonic value of simply tasting sweetness in the ventral striatum and the postingestive rewarding effects of sugar in the dorsal striatum (6).

A heightened preference for intense sweetness is innate and a hallmark of youth (7). From late adolescence to adulthood, however, sweetness preference declines in both rodents (8) and people (7,9–11). In addition, data from studies conducted in rodent models demonstrate

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that the decline in sweetness preference is attenuated by obesity (8). The mechanisms responsible for the age-related decline in sweetness preference and the alteration in sweetness preference associated with obesity are not known (12). The main purpose of this study was to test the hypothesis that the age-related decline in sweet preferences is directly related to the age-related decline in striatal D_2 receptors (D2R) and that this relationship is altered in people with obesity.

RESEARCH DESIGN AND METHODS

Participants

Twenty-four subjects with obesity (BMI $\geq$30.0 kg/m^2) and 20 subjects without obesity (BMI <26.0 kg/m^2) between the ages of 18 and 40 years old (Table 1) provided written informed consent and participated in this study, which was approved by the institutional review board of the Washington University School of Medicine in St. Louis. Selected data from these subjects have been reported previously (13–15). Potential subjects completed a comprehensive medical evaluation that included an oral glucose tolerance test (OGTT); those who had diabetes, smoked tobacco, were taking medications that affect dopamine function, had an IQ <80, or had neurological conditions including parkinsonism, lifetime psychosis, mania, substance dependence, major depression, social phobia, or eating disorders and panic disorders determined by neurological examination and psychiatric interview were excluded.

Taste Testing

The following tests were performed ~1 h after subjects completed the OGTT and consumed a standardized light snack.

Table 1—Subject characteristics

	Without obesity (n = 19)	With obesity (n = 22)	P
Age, years	28.3 ± 5.4	31.2 ± 6.3	0.12
Sex, n (men/women)	4/15	3/19	0.41
Height, cm	170.0 ± 8.4	166.8 ± 8.4	0.23
Weight, kg	64.5 ± 9.9	111.9 ± 17.9	<0.001
BMI, kg/m^2	22.5 ± 2.4	40.3 ± 5.0	<0.001
Glucose, mg/dL	89.2 ± 6.3	97.5 ± 7.0	<0.001
Insulin, µIU/mL	5.5 ± 3.1	17.0 ± 8.8	<0.001
HOMA of insulin resistance	1.2 ± 0.7	4.1 ± 2.2	<0.001
D2R BP$_{ND}$			
Dorsal striatum	8.13 ± 1.0	8.11 ± 1.1	0.95
Nucleus accumbens	2.11 ± 0.2	1.99 ± 0.4	0.21
Race (%)			0.08
White	84	54	
Black	11	41	
Other/mixed	5	5	
Education, years	16.1 ± 1.6	15.1 ± 1.8	0.08

Data are mean ± SD, unless otherwise indicated.

Sucrose Intensity Perception

To ensure differences in preferences were not confounded by differences in perception of stimuli strength, we determined subjects' perception of sweet taste intensity across a range of sucrose concentrations by using the general label magnitude scale (16), as previously described (17).

Sucrose Preferences

To determine the subjects' most preferred intensity of sweetness, we used the Monell two-series, forced-choice tracking procedure (11). Subjects were presented with pairs of solutions that differed in sucrose concentration (3%–36% w/v), and preferences were determined as previously described (11,17).

Positron Emission Tomography and MRI Acquisition and Analyses

On a separate visit, an average of 13.9 days (SD 17.1) after taste testing, subjects underwent functional MRI and 2-h positron emission tomography (PET) scans. Methods for (N-[^{11}C] methyl)benperidol ([^{11}C]NMB) synthesis, MRI, and PET scan acquisitions and preprocessing were described previously (13,14). Each participant received an intravenous infusion of a D2R-selective radioligand not sensitive to endogenous dopamine, [^{11}C]NMB (6.4–18.1 mCi) over 20 s. [^{11}C]NMB purity was $\geq$96% and specific activity was $\geq$1,066 Ci/mmol (39 TBq/mmol). PET scans were done with the Siemens/CTI ECAT EXACT HR+ tomograph (18). Emission data were collected in 3D mode for 2 h with a total of 30 frames: 3×1 min, 4×2 min, 3×3 min, and 20×5 min. Transaxial and axial spatial resolution at slice center are 4.3 mm and 4.1 mm full width at half maximum in 3D mode.

The methods for our region of interest–based analyses are described previously (13,14). We used FreeSurfer for segmentation of striatal regions (19). To limit multiple comparisons, we averaged D2R specific binding (nondisplaceable binding potential [BP$_{ND}$]) across left and right hemispheres for each region of interest. Putamen and caudate D2R BP$_{ND}$ values were averaged to obtain a composite dorsal striatal BP$_{ND}$, and nucleus accumbens D2R BP$_{ND}$ was used to determine ventral striatal BP$_{ND}$. The midbrain region of each individual's magnetization-prepared rapid gradient-echo was traced as previously described (13).

Statistical Analyses

The statistical significance of values between groups was evaluated by using Pearson's χ^2 or unpaired t test as appropriate, and differences in sweetness intensity perception between groups was evaluated by using a mixed ANOVA. We used separate linear regression models for dorsal and ventral striatum to analyze the ability of age and D2R BP$_{ND}$ to predict sucrose preferences. Age $\times$ group and D2R BP$_{ND}$ $\times$ group interactions were included in the model to test the hypothesis that group affected the strength of relationships between main factors. Analyses were repeated using race and sex as covariates

in step 1 of hierarchical multiple linear regression models. Data in the tables and figures are presented as mean ± SD, unless otherwise indicated.

RESULTS

Subject Characteristics

Subjects with and without obesity did not significantly differ in age, height, years of education, sex, or race distribution, but subjects with obesity had higher plasma glucose and insulin concentrations and were more insulin resistant, as indicated by the HOMA of insulin resistance score. As previously reported (15), both groups had similar striatal BP_{ND} (Table 1). With the exception of two participants who were overweight (BMI 25.9 and 25.1 kg/m²), all other subjects in the group without obesity were normal weight (BMI 18.6–24.6 kg/m²). Two of the 24 subjects with obesity were excluded from the analyses because their sucrose preferences testing was unreliable, and one subject without obesity was excluded because his sucrose preference was more than 2 SD above the group mean and his sweetness perception was markedly blunted.

Sweet Taste Testing

Sucrose preferences ($P = 0.41$) (Fig. 1A) and perception of sweetness intensity were similar between groups (group × sucrose concentration interaction $P = 0.37$) (Fig. 1B).

Relationships Among Age, Central D2Rs, and Sucrose Preferences

Consistent with our previous finding in a subset of these subjects (13), there was an age-related decline in dorsal ($r = -0.42$; $P < 0.01$), but not ventral ($r = -0.23$; $P = 0.14$), D2R BP_{ND} in both groups. However, the relationship between age, striatal D2R BP_{ND}, and sucrose preferences were markedly different in groups with and without obesity (model for dorsal striatum: $R^2 = 0.32$, $F_{4,36} = 4.32$, $P < 0.01$; both interactions: dorsal D2R BP_{ND} × group and age × group had a $P \leq 0.01$) (model for ventral

striatum: $R^2 = 0.28$; $F_{4,36} = 3.53$; $P = 0.02$; ventral D2R BP_{ND} × group interaction had a $P = 0.03$; age × group interaction had a $P = 0.06$). There was a negative linear relationship between age and sucrose preferences and between both dorsal and ventral D2R BP_{ND} and sucrose preferences in subjects without obesity; age and dorsal striatal D2R BP_{ND} accounted for 52% (Fig. 2A and B) and age and ventral striatal D2R BP_{ND} accounted for 40% (Fig. 3A and B) of the individual differences in sucrose preferences. These associations remained significant when controlling for race and sex in a hierarchical regression model. In contrast, there were no significant relationships between age and sucrose preferences (Figs. 2C and 3C) or between D2R BP_{ND} and sucrose preferences (Figs. 2D and 3D) in subjects with obesity.

DISCUSSION

The primary findings of this study are that subjects with obesity lack the normal associations between age and sucrose preferences and between striatal D2R BP_{ND} and sucrose preferences. Additionally, age-related decline in D2R BP_{ND} is not directly related to the age-related decline in sucrose preferences. Instead, lower sucrose preference in subjects without obesity related both to increased striatal D2R BP_{ND} and older age, explaining up to 52% of individual variance in sucrose preference.

Our findings in subjects without obesity contribute to the understanding of the important role of dopamine on feeding behavior and food reward (20,21). Previous neuroimaging studies in healthy lean people report that dopamine release in dorsal striatum correlates positively with subjective ratings of wanting a food (20) or pleasure experienced from eating a favorite food (21). Here we found that lower striatal D2R BP_{ND} relates to preferences for more intense sweetness, which supports observations that patients with Parkinson disease, a neurodegenerative disorder characterized by striatal presynaptic dopamine
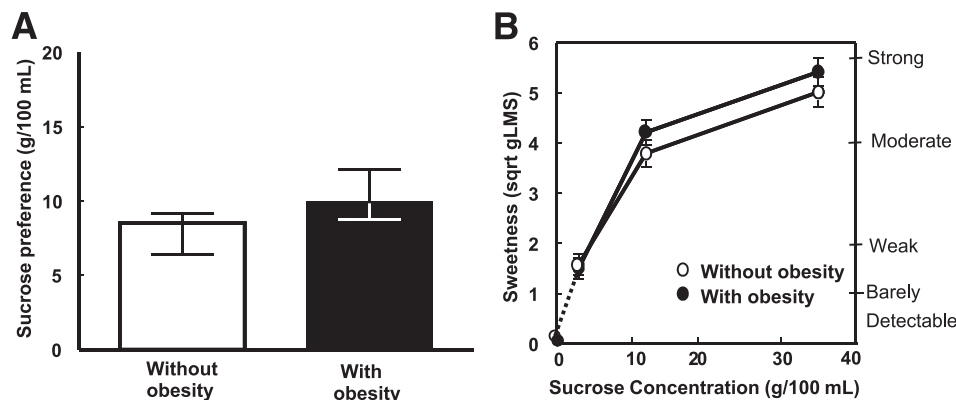

Figure 1—Sucrose preferences (A) and perceived sweetness of increasing sucrose concentrations (0%, 3%, 12%, and 36% w/v) (B) do not differ between subjects without and with obesity. Both groups similarly perceived progressively increasing sweetness intensity with increasing sucrose concentrations ($P < 0.0001$). Data are presented as geometric mean ± geometric SE for sucrose preferences and as mean ± SEM for sweetness intensity. sqrt gLMS, square root of ratings made on the general label magnitude scale.
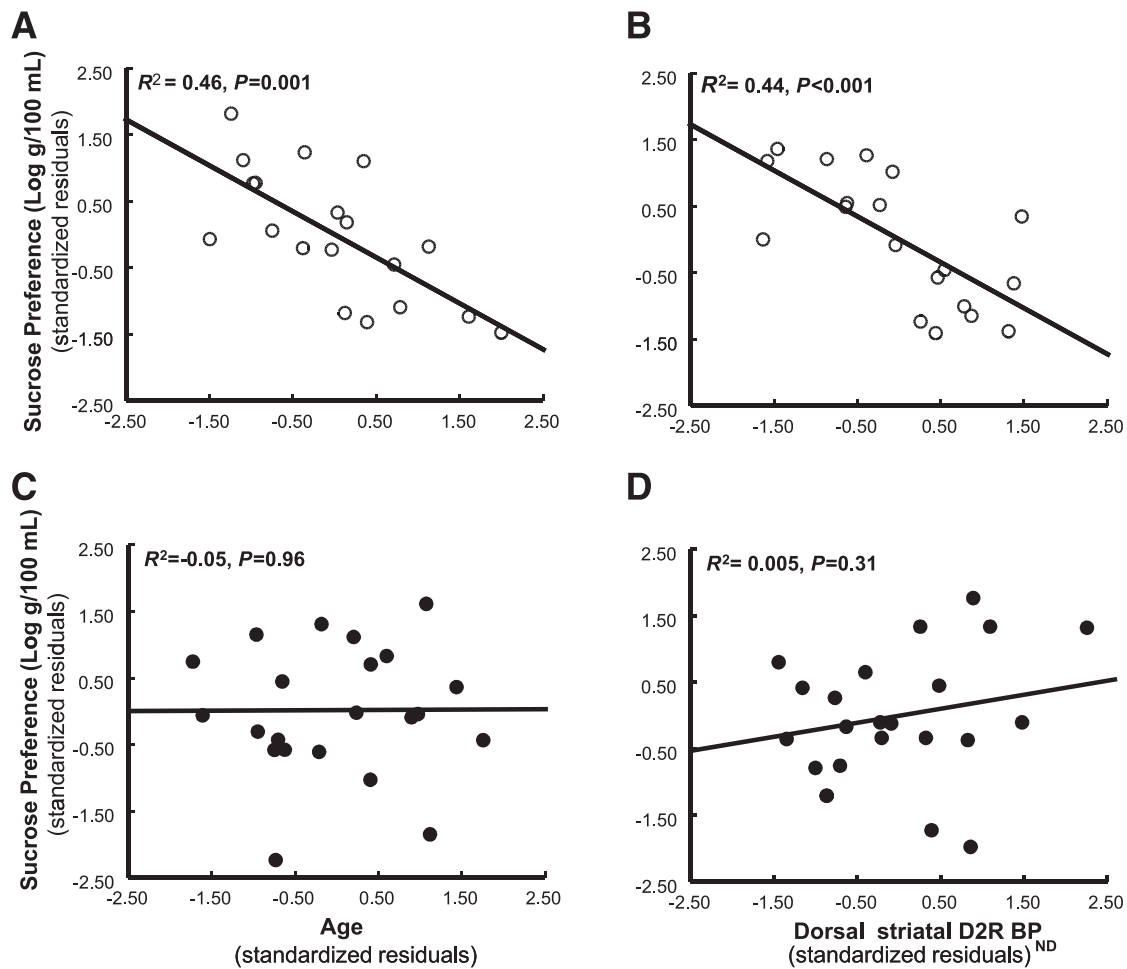
Figure 2—Preferences for higher sucrose concentrations were related to younger age (*A*) and lower dorsal striatal D2R BP_{ND} (*B*) in subjects without obesity (open symbols). Together, age and dorsal striatal D2R BP_{ND} accounted for 52% of the individual differences in sucrose preferences. In contrast, sucrose preferences did not associate with age (*C*) or with dorsal striatal D2R BP_{ND} (*D*) in subjects with obesity (closed symbols). Data points are standardized residuals of partial correlations after controlling for D2R BP_{ND} in panels *A* and *C* and after controlling for age in panels *B* and *D*.

deficiency, exhibit greater liking for higher sucrose concentrations (22) and correlates with data from rodent models that show that treatment with dopamine receptor antagonists cause a shift in sweet preferences toward more concentrated sucrose solutions (23). By contrast, sucrose preference did not relate to striatal D2R BP_{ND} in subjects with obesity. The mechanism underlying this lack of association in subjects with obesity is unknown. Our data suggest one more type of dopaminergic disruption associated with obesity. However, whether this dopaminergic disruption truly relates to having a BMI >30 kg/m^2 or to other characteristics that may be clustered with obesity, such as having a specific type of diet (e.g., high-fat diet) or markers of metabolic syndrome (e.g., insulin resistance or hyperleptinemia), is unknown.

Several research studies tried to determine whether subjects with obesity respond to sweetness differently from subjects without obesity, with conflicting results

(16). The disruption in subjects with obesity of the well-known age-related decline in sucrose preference suggests that age could be an important factor contributing to inconsistency in the literature of sweetness preferences in obesity. That is, differences may be negligible when sucrose preferences are measured in young adulthood, as we found, but may become more apparent in older populations. The age consideration may also apply to D2R differences; however, in this same population, we reported no D2R differences between groups with and without obesity (13).

Our findings in subjects without obesity support the known age-related decline in sweet preferences (7,9,11) but do not help explain the mechanism(s) underlying such a developmental shift. A previous study in 11- to 15-year-old children found that preferences for high versus low sucrose concentrations related to differential amounts of a biomarker of bone growth in urine, suggesting that biochemical changes controlling linear growth mediate developmental changes in sugar preferences (10). The
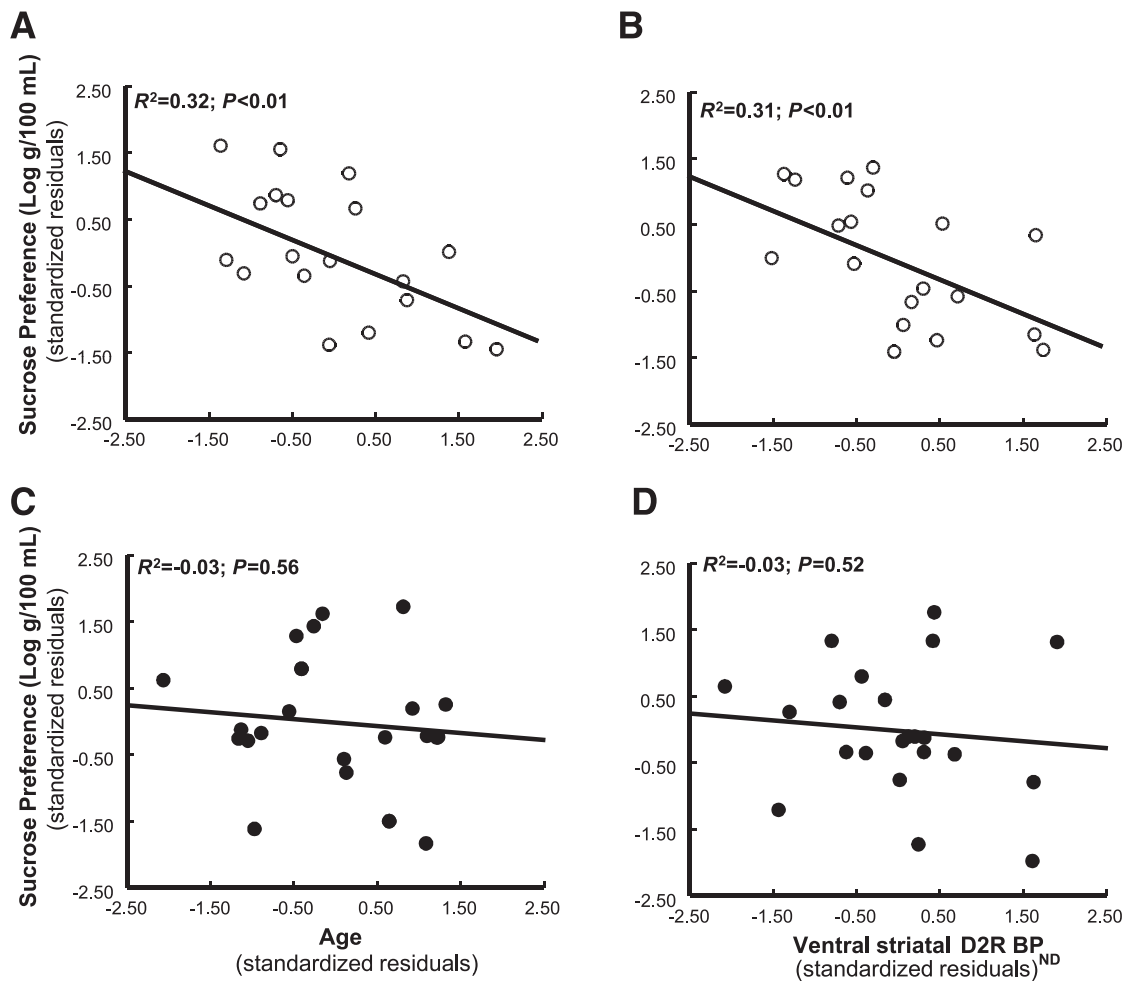
Figure 3—Preferences for higher sucrose concentrations were related to younger age (A) and lower nucleus accumbens (ventral striatum) D2R BP_{ND} (B) in subjects without obesity (open symbols). Together, age and ventral striatal D2R BP_{ND} accounted for 40% of the individual differences in sucrose preferences. In contrast, sucrose preferences did not associate with age (C) or with ventral striatal D2R BP_{ND} (D) in subjects with obesity (closed symbols). Data points are standardized residuals of partial correlations after controlling for D2R BP_{ND} in panels A and C and after controlling for age in panels B and D.

strong negative association between age and sucrose preference found in our nonobese subjects, who were between 20 and 40 years old and have presumably completed their linear growth, suggests that some other, as-yet-unknown mechanism contributes to age-related changes in sucrose preferences and that this mechanism is disrupted in obesity.

Our study has several important limitations. It is possible that our results were influenced by differences in race between groups and by the majority of women in both groups, as people of African American descent generally prefer higher concentrations of sucrose than people of Caucasian descent (9) and there could be sex-related variations in taste perception (24). However, the statistical significance of the relationships between any of our outcome measures do not change when using statistical analyses that control for race and sex. Therefore, it is unlikely that race or sex significantly influenced our conclusions. In addition, we cannot exclude the possibility

that gonadal hormone–related variations in taste perception (24) affected our results because we did not measure plasma hormone concentrations and did not control for the menstrual cycle phase. Finally, these results will require replication because of the novel nature of our findings and the small sample on which they are based.

In summary, both striatal D2R BP_{ND} and age are negatively correlated with sucrose preferences in subjects without obesity, but these associations are absent in subjects with obesity. Our data suggest that the age-related decline in D2R is not directly linked to the age-related decline in sweetness preferences, suggesting that other, as-yet-unknown mechanisms are involved and that these mechanisms are disrupted in obesity.

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