Feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in healthy human volunteers

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Abstract

Seven healthy subjects underwent two [^{11}C]raclopride positron emission tomography (PET) scans, one following a 16-h fast and the other after consumption of a favorite meal (following a 16-h fast) in counterbalanced fashion. Before and after each scan subjects gave ratings of hunger/fullness and desire to eat. In addition, meal pleasantness ratings were collected immediately after consumption of the favorite meal. PET data were analyzed using brain parametric maps to generate regions of statistically significant change, as well as regions of interest manually drawn on each individual's coregistered anatomical image. [^{11}C]Raclopride binding potential was compared across the two states (hungry and full). A significant reduction in binding potential was observed in the full compared to the hungry state in the dorsal putamen and caudate nucleus, indicative of dopamine release. There were no changes elsewhere in the striatum. A correlation was observed between the reduction in [^{11}C]raclopride binding and meal pleasantness ratings, but not with desire to eat (hunger) or satiety after eating. These results suggest that feeding is associated with dopamine release in the dorsal, but not the ventral striatum, and that the amount of dopamine released correlates with the degree of experienced pleasure.
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Introduction

Dopamine is thought to be involved in the reinforcing effects of food, drugs of abuse, and electrical brain stimulation. An influential theory, the anhedonia hypothesis, posits that addictive drugs produce their reinforcing effects by interacting with the neural circuitry that originally evolved to subserve feeding behavior and that dopamine may mediate the pleasurable aspects of natural rewards (Wise, 1996a, 1996b). Much of the support for this theory comes from animal studies showing that both addictive drugs and natural rewards promote dopamine release in the nucleus accumbens (NAc).

However, there is evidence that undermines the anhedonia hypothesis. For example, food-induced activation of dopamine neurons is significantly blunted or absent if the food reward is expected (Schultz, 1998), or if a similar food has been administered to the animal in the past 24 h (Bassareo and Di Chiara, 1997). Also, dopamine depletion or blockade does not appear to diminish pleasurable responses to palatable foods in animals or humans (Berridge and Robinson, 1998). These and other findings have given rise to an alternative theory of dopamine function, emphasizing its role in motivation rather than pleasure (Bindra, 1978; Berridge and Robinson, 1998). Finally, although dopamine may be involved in processing both natural and drug rewards, it could be acting at different sites. There is recent experimental evidence that it is in the dorsal striatum that dopaminergic action is crucial for feeding behavior (Beninger and Ranaldi, 1993; Szczypka et al., 2001), whereas abused drugs tend to promote dopamine release in the ventral striatum (Di Chiara and Imperato, 1988). This distinction is important because it implies that there may be different neurophysiological mechanisms underlying the responses to natural compared to artificial rewards. We therefore un-
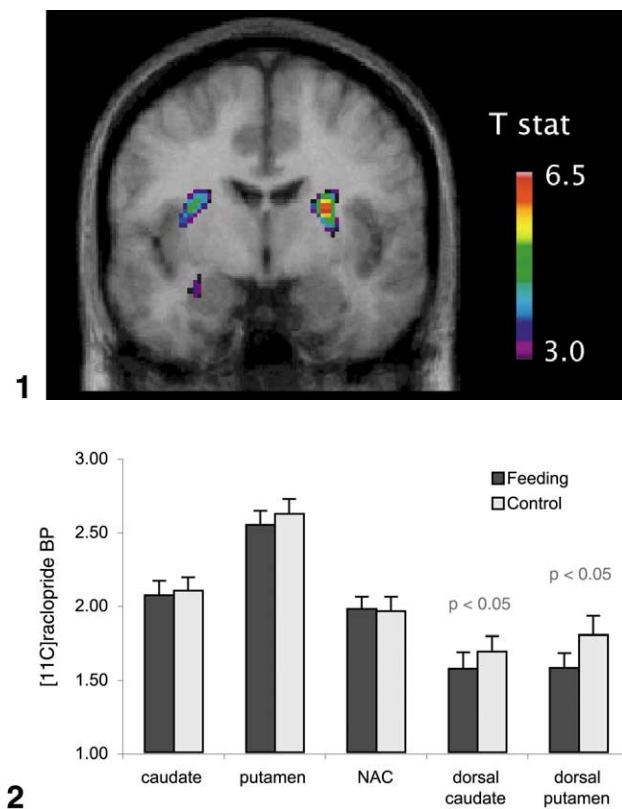
Fig. 1. Dopamine release induced by feeding. Coronal section from the T-map of statistically significant reductions in [11C]raclopride BP following feeding. The colorbar represents the *t* statistic values.

Fig. 2. Region of interest analysis. Mean [11C]raclopride BP values from the region-of-interest analysis (see experimental procedures for details). Error bars represent the standard error of the mean. The change in binding was statistically significant in the dorsal caudate and dorsal putamen only. All data represent the mean of the ROI from the left and right hemispheres.

dertook the current study to answer two questions: Does a pleasant food stimulus cause dopamine release in the striatum? And, if so, is the amount of dopamine released related to either pleasure or motivation to eat?

Here we present evidence that, in humans, eating a favorite meal is associated with dopamine release in the dorsal striatum and that the amount of dopamine released is proportional to the perceived pleasantness of the meal. Seven lean healthy subjects underwent two [11C]raclopride PET scans, one after an overnight fast and the other after consumption of subject's "favorite meal." Subjective ratings of food pleasantness, hunger and satiety, and mood state were obtained for correlation with the PET results.

Methods

Subjects

Seven volunteers (two males) participated. All were free of any current or previous neurological or psychiatric illness, including obesity and drug abuse (other than nicotine),

and all gave written informed consent to participate in the study, which was approved by the Montreal Neurological Institute Research Ethics Board. Two subjects were smokers (subjects number 4 and 5) and both were asked not to alter their smoking habits prior to the scans. Smokers were not excluded as we have previously shown that acute nicotine does not alter [11C]raclopride binding in humans (Barrett et al., 2001).

Procedure

Each subject underwent two [11C]raclopride PET scans, one at approximately 11:00 A.M. following an overnight 16-h fast and one at approximately 2:30 P.M. immediately after eating, also following an overnight fast. Subjects were allowed only to drink water and their usual amounts of coffee during the fasting period. Scan order was counterbalanced. Subjects started eating 30 min before the [11C]raclopride injection and were allowed to eat for 15 min. Subjects were asked to verbally rate their level of hunger/satiety on a scale of −10 ("starving") to +10 ("extremely full") immediately before and 15 min after eating. After eating, they were also asked to rate the pleasantness of the meal (from 0 to 10, with 0 being neutral). Mood at the time of scanning was measured using the profile of mood states (POMS), a 72-item questionnaire that yields a score on six mood categories, namely clearheaded, confident, agreeable, energetic, elated, and composed (McNair et al., 1992).

PET image acquisition and analysis

PET scans were obtained with a CTI/Siemens HR + 63-slice tomograph operated in 3D acquisition mode, yielding images of resolution $4.8 \times 4.8 \times 5.6$ mm full width at half maximum at the center of the field of view. A transmission scan with a rotating rod source was performed for attenuation correction, followed by injection of 10 mCi of the D2 receptor ligand [11C]raclopride into the antecubital vein over 1 min. PET emission data were then acquired over 60 min in 26 time frames of progressively longer duration. All subjects also underwent high-resolution T1-weighted magnetic resonance imaging (MRI) scan on a separate day (1 mm³ acquisition, TR = 9.7 ms, TE = 4 ms, flip = 12°, FOV = 250, matrix = 256 × 256).

PET frames were summed for coregistration with the MRI (Woods et al., 1993) and transformation into standardized stereotaxic space (Talairach and Tournoux, 1988) by means of automated feature matching to the MNI template (Collins et al., 1994). Voxelwise [11C]raclopride binding potential (BP) was calculated using a simplified reference tissue method (Lammertsma and Hume, 1996; Gunn et al., 1997), with the cerebellum as reference region, to generate statistical parametric images of change in binding (Aston et al., 2000). It is assumed that a reduction in [11C]raclopride BP is indicative of an increase in extracellular dopamine concentration (Endres et al., 1997; Hartvig et al., 1997;
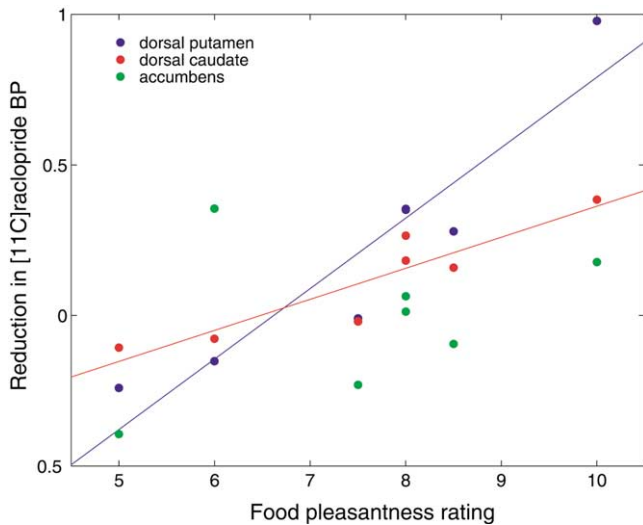
Fig. 3. Correlation between pleasantness and dopamine release. Plots of the rated pleasantness of the meal versus the reduction in [^{11}C]raclopride BP in the dorsal putamen, caudate nucleus, and nucleus accumbens as determined from region-of-interest analysis. Data from the left and right hemispheres were combined. (NB: for the dorsal putamen there are two superimposed data points at $x = 8$.)

Laruelle et al., 1997). Simulation studies have shown that the method we use is insensitive to physiological changes in regional cerebral blood flow (Aston et al., 2000). We use a cutoff of $t = 4.2$, which corresponds to a corrected P value of 0.05 for a search volume equal to the striatum (Worsley et al., 1996). Only the striatum is analyzed, as [^{11}C]raclopride does not bind to extrastriatal sites with sufficient specificity to permit quantification. Region-of-interest (ROI) analysis was used to confirm the statistical parametric map results and perform correlational analyses. ROI were drawn manually on transverse slices from each subject's MRI transformed into stereotaxic space on the dorsal caudate nucleus, dorsal putamen, central caudate nucleus and putamen, and ventral striatum bilaterally. We used stereotaxic rather than native space in order to achieve relatively standardized ROI placement for each subject, using the standardized coordinates as a guide. The rostrocaudal extent of the ROI relative to the anterior commissure was approximately the same for all subjects, $z = 18$ to 22 mm for the dorsal caudate, $z = 14$ to 16 mm for the dorsal putamen, $z = 6$ to 16 mm for the central caudate, $z = 4$ to 10 mm for the central putamen, and $z = -4$ to -8 mm for ventral striatum, corresponding approximately to the NAc (Talairach and Tournoux, 1988). The boundaries for each of the ROI were drawn within the gray matter of each nucleus to minimize partial volume effects. ROI drawn on five consecutive 1-mm slices in cerebellum served as the reference region.

Results

Statistical parametric maps (Fig. 1) of the change in [^{11}C]raclopride BP showed a significant reduction in the

post-feeding condition in the dorsal putamen bilaterally (peak coordinates, left: -27, 2, 16, t: 4.8; right: -28, -4, 18, t: 6.4) and in the right dorsal caudate nucleus (coordinates: 12, 10, 20, t: 4.2). There were no changes elsewhere in the striatum. This was confirmed with the ROI drawn on the subjects' MRI scans (Table 2; Fig. 2). The absolute difference in [^{11}C]raclopride BP between the post-meal and fasting scans was, for the central caudate nucleus, 0.03 (1.5%, NS, by paired t test); for the central putamen, 0.07 (2.8%, NS); for the ventral striatum, -0.02 (-0.8%, NS); for the dorsal caudate, 0.11 (6.8%, $P = 0.02$); and for the dorsal putamen, 0.22 (12.4%, $P = 0.03$). The statistical map was overlayed on average BP maps of all subjects to confirm that the statistical peaks were within the areas of specific [^{11}C]raclopride binding. The lower [^{11}C]raclopride BP in the post-meal scans is indicative of dopamine release in relation to eating (Endres et al., 1997; Hartvig et al., 1997; Laruelle et al., 1997).

We performed stepwise linear regression analyses to determine the relationship between change in [^{11}C]raclopride BP in the dorsal striatum and subjective ratings (meal pleasantness, hunger prior to eating, or satiety after eating). Pleasantness ratings predicted 82% of the variance of the change in BP [$F(1, 6)$ 23.1; $P = 0.005$] in the right dorsal caudate, and 87% of the variance of the change in BP [$F(1, 6)$ 34.5; $P = 0.002$] in the dorsal putamen (left and right combined) (Fig. 3). Inspection of Fig. 3 suggests that one of the data points for the dorsal putamen might have had undue influence on the correlation (the point with the largest BP change). Therefore, we repeated the analysis without this data point and still obtained a significant correlation [$F(1, 5)$ 20.3; $P = 0.01$]. There was no correlation between pleasantness ratings and BP change in the central caudate or putamen or the ventral striatum. No relationship was observed between change in BP and hunger, satiety, or difference between hunger and satiety ratings in any region. The variance inflation factors were less than five for all of the independent variables (pleasantness, hunger, fullness, and difference between hunger and satiety), indicating that multicolinearity was not present. Additionally, although the amount and type of food eaten by the subjects differed and was not systematically measured, consideration of the meal content suggests that total energy consumption or amount of food eaten did not correlate with pleasantness ratings (Table 1). This is illustrated most clearly by the fact that the subject with the highest pleasantness rating and BP change and the subject with the lowest pleasantness rating and BP change coincidentally ate the same meal (sushi) (Table 1). We also performed a multiple-regression analysis with the change in POMS scores using a model including meal pleasantness rating and the six POMS variables (clearheaded, confident, agreeable, energetic, elated, and composed). Meal pleasantness was the most significant predictor of BP change, and none of the POMS variables contributed significantly to the model ($P > 0.05$). This suggests that meal pleasantness was

Table 1
Subjective ratings[a]

Subject	Satiety before meal	Satiety after meal	Difference	Meal pleasantness	Meal
1	−8	8.5	16.5	7.5	Chinese food (General Tao chicken, rice)
2	−9	9	18	8.5	Indian food (nan bread, vegetable curry, rice)
3	−7	8	15	8	Greek salad, grilled vegetables, octopus
4	−7	4	11	6	Beef ribs, fries, coleslaw and apple pie
5	−9	4	13	10	Sushi (10 pieces)
6	−8	7	15	5	Sushi (10 pieces)
7	−5	5	10	8	Fried chicken, fries

[a] See text for details.

related to the change in BP independently of a general change in well-being or mood.

Discussion

Consumption of a favorite meal by healthy lean human volunteers was associated with bilateral reduction in [11C]raclopride BP in the dorsal putamen and caudate (Figs. 1 and 2) when compared to the fasting state. Moreover, the change in [11C]raclopride BP in these areas correlated with meal pleasantness ratings (Fig. 3), suggesting that dopamine release in the dorsal striatum is related to food reward. There was no correlation between the change in [11C]raclopride BP in any part of the striatum and the premeal hunger rating or the difference in hunger ratings before and after eating, indicating that dopamine release, as measured here, was not related to motivation to eat or to the degree of satiety induced by the meal. Notably, no change in [11C]raclopride BP was observed in the ventral striatum, including the NAc (Fig. 2).

Numerous animal studies have implicated dopamine in feeding behavior. Animals with lesions of the dopamine system do not eat and usually die from starvation (Ungerstedt, 1971). Feeding is associated with dopamine release in the striatum as detected by in vivo microdialysis (Hernandez and Hoebel, 1988). Dopamine antagonists impair the ability of food to act as a reinforcer (Wise et al., 1978) and may reduce the rewarding value of food (Hsiao and Smith, 1995). Also, food rewards have been shown to act in synergy with addictive drugs and intracranial self-stimulation (Conover and Shizgal, 1994), both of which are thought to exert their reinforcing effects through actions on the dopamine system.

These studies led to the theory that food reward, like drug reward, mostly involved the ventral striatum, which may be at variance with our current findings. The dorsal and ventral striatum can be separated functionally and anatomically (Moore and Bloom, 1978; Heimer et al., 1982; Haber et al., 2000), and several animal studies show that ingestion of palatable foods is associated with dopamine release in the NAc (Heffner et al., 1980; Hernandez and Hoebel, 1988), which is part of the ventral striatum. However, the extensive

animal literature suggests that the NAc dopamine response to food is complex and is modulated by hunger, previous exposure to food or appetitive stimuli, the delay between appetitive stimuli and reward, the reinforcement schedule, and the nature and delivery rate of appetitive stimuli or of the food reward itself (Wilson et al., 1995; Richardson and Gratton, 1996; Bassareo and Di Chiara, 1999). Moreover, evidence from animal studies suggests that it is the dorsal rather than the ventral striatum that plays the key role in feeding. For example, 6-hydroxydopamine lesions of the NAc in rats do not reduce food consumption (Salamone et al., 1993), lesions of the dopamine projection to the NAc impair lever pressing for cocaine, but not for food (Roberts et al., 1977), whereas microinjections of a dopamine antagonist into the caudate-putamen but not the NAc produce declines in food-rewarded lever pressing (Beninger and Ranaldi, 1993). Finally, virally mediated restoration of dopamine production in dopamine deficient mice reverses aphagia only when the caudate-putamen, and not the NAc, is targeted (Szczypka et al., 2001). In addition to the concordance with animal studies implicating the dorsal striatum in feeding, our current findings are also consistent with our previous human PET study, where we reported that regional cerebral blood flow measured while eating chocolate correlated with pleasantness ratings in the dorsal caudate and putamen, but not in the NAc (Small et al., 2001).

Nonetheless, our results do not exclude a role for NAc dopamine in feeding. Salamone et al. have suggested that NAc dopamine is most involved in the choice of an action in response to sensory inputs and motivational states (Salamone et al., 1997). If this is true, it is possible that we did not observe changes in the NAc because receipt of food reward was not contingent upon a behavioral response, apart from eating a served meal. Another possibility is that dopamine release occurred in the NAc in both of our testing conditions. During the fasting scan, subjects were hungry and likely looking forward to eating, which they knew they could do immediately after the scan. Indeed, NAc dopamine release has been described in animals during the anticipation of a meal (Phillips et al., 1993; Kiyatkin and Gratton, 1994; Wilson et al., 1995). However, the fact that we did not detect a difference in the ventral striatum is unlikely to be

Table 2
[^{11}C]raclopride binding potential from the regions of interest

Subject	Caudate	Putamen	NAC	Dorsal caudate	Dorsal putamen
Postmeal					
1	1.52	2.06	1.98	1.07	1.27
2	2.08	2.54	1.76	1.50	1.32
3	1.80	2.47	1.82	1.08	1.36
4	2.75	3.22	2.53	2.26	2.29
5	2.11	2.69	1.72	1.79	1.88
6	2.18	2.62	2.23	1.70	1.57
7	2.02	2.20	1.77	1.59	1.31
Mean (SD)	2.06 (0.37)	2.54 (0.36)	1.97 (0.31)	1.57 (0.42)	1.57 (0.38)
Premeal					
1	1.41	1.92	1.58	0.98	1.03
2	2.08	2.49	1.77	1.68	1.67
3	2.01	2.79	2.00	1.46	2.34
4	2.52	3.16	2.30	2.24	2.28
5	2.17	2.89	1.63	1.95	2.16
6	2.28	2.61	2.58	1.62	1.42
7	2.21	2.45	1.83	1.85	1.67
Mean (SD)	2.10 (0.34)	2.62 (0.38)	1.96 (0.36)	1.68 (0.39)	1.80 (0.49)

due to an inability of the PET technique to detect changes in [^{11}C]raclopride BP in this region, as we have previously used the same method and PET camera to demonstrate dopamine release confined to the ventral striatum in human subjects receiving low doses of amphetamine (Leyton et al., 2002) or alcohol by mouth (Boileau et al., 2003).

Interestingly, the reduction in [^{11}C]raclopride BP that we observed correlated with the subjective pleasantness of the meal, but not with hunger or satiety ratings. Based on combined PET microdialysis studies showing that the reduction in benzamide binding is proportional to the increase in extrasynaptic dopamine (Endres et al., 1997; Laruelle et al., 1997), we conclude that the quantity of dopamine released during eating was proportional to the pleasantness of the meal. This finding would appear to be consistent with the theory that the role of dopamine in reward is to mediate the hedonic aspect, or pleasure, of the rewarding stimulus (Wise, 1996a, 1996b). However, this theory has been criticized based on the fact that lesions of dopamine neurons or dopamine receptor blockade in animals do not appear to impair taste reactivity measures (e.g., tongue protrusions and paw licks), which are thought to denote pleasurable reactions (Berridge and Robinson, 1998). An alternative explanation that reconciles these facts with our current findings is that it is the experience of pleasure that leads to dopamine release. In rats, injections of opioid agonists into the shell of the NAc increase hedonic reactions to food (Pecina and Berridge, 2000), although opioid antagonists block dopamine release in this same brain structure in response to food reward (Tanda and Di Chiara, 1998). This suggests that cortical signals that depend on affective evaluations could promote dopamine neuron firing via opioid transmitters acting on interneurons in the ventral tegmen-

tum, which would explain why we found a correlation between pleasantness and striatal dopamine release.

Although this is the first evidence that dopamine is released during feeding in humans, Wang and colleagues have used PET to show that the body mass index of obese individuals is negatively correlated with baseline [^{11}C]raclopride BP (Wang et al., 2001). Their interpretation is that obese individuals have reduced D2 receptors in the striatum, which may perpetuate pathological eating as a means to compensate for the decreased function of reward circuits. An alternative explanation is that overeating results in a downregulation of D2 receptors. Our results are consistent with either interpretation. The same group also used PET and [^{11}C]raclopride to measure dopamine release in response to food-related visual, gustatory, and olfactory cues in hungry individuals (Volkow et al., 2002). The study was similar to ours in that subjects were food-deprived prior to testing, and subjects' favorite foods were chosen; however, they did not consume the food during these experiments. Another difference is that the data were analyzed with seemingly relatively large regions of interest drawn without the benefit of coregistered MRI images. Although differences in [^{11}C]raclopride binding similar to the ones reported here were detected when comparing food to no-food stimulation, these were not statistically significant. It may be that our approach using voxelwise statistical parametric mapping and more precise delineation of the dorsal striatum using the MRI for ROI analysis is more sensitive to spatially restricted changes in dopamine release. Indeed, our ROI over the central part of the caudate and putamen showed no significant difference in tracer binding (Table 2). Another possibility to explain the apparent discrepancy is that food

consumption leads to greater dopamine release than simple exposure to food-related stimuli.

The PET methodology has limitations. It is thought that the reduction in [^{11}C]raclopride binding that occurs following dopamine release is due to internalization of D2 receptors (Laruelle, 2000; Sun et al., 2003), an effect that lasts considerably longer than the increase in synaptic dopamine levels. Therefore, although the approach used here allows one to determine if dopamine release did occur, it has relatively poor temporal resolution, so that it is not possible to say at what time point dopamine release occurred in response to feeding, nor to which aspect of feeding. This must be borne in mind when comparing our results to those of numerous animal experiments of feeding, which have demonstrated significant variations in dopamine response with sometimes subtle changes in study design. Considerable controversy exists, for example, on whether dopamine release is mostly linked to the anticipation or the consumption of food (Salamone et al., 1997; Berridge and Robinson, 1998). Moreover, we cannot make any claims with respect to dopamine release in extrastriatal regions such as the frontal cortex, which has been implicated in feeding (Bassareo and Di Chiara, 1997), because [^{11}C]raclopride does not bind specifically outside the striatum. Finally, one could have envisaged a design in which subjects were fed prior to both scans, once with a neutral meal and once with a favorite meal, in order to more clearly determine the role of pleasantness in dopamine release.

In conclusion, this study reports the first evidence of feeding-induced dopamine release in humans and suggests that food reward is related to dopamine action in the dorsal as opposed to the ventral striatum. These results provide a baseline upon which future studies of addiction and eating disorders may be compared.

Acknowledgments

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