Increased Dopamine D2/D3 Receptor Binding After Recovery from Anorexia Nervosa Measured by Positron Emission Tomography and [^{11}C]Raclopride

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Background: *Several lines of evidence support the possibility that disturbances of dopamine (DA) function could contribute to alterations of weight, feeding, motor activity, and reward in anorexia nervosa (AN).*

Methods: *To assess possibly trait-related disturbances but avoid confounding effects of malnutrition, 10 women who were recovered from AN (REC AN) were compared with 12 healthy control women (CW). Positron emission tomography with [^{11}C]raclopride was used to assess DA D2/D3 receptor binding.*

Results: *The women who were recovered from AN had significantly higher [^{11}C]raclopride binding potential in the antero-ventral striatum than CW. For REC AN, [^{11}C]raclopride binding potential was positively related to harm avoidance in the dorsal caudate and dorsal putamen.*

Conclusions: *These data lend support for the possibility that decreased intrasynaptic DA concentration or increased D2/D3 receptor density or affinity is associated with AN and might contribute to the characteristic harm avoidance or increased physical activity found in AN. Most intriguing is the possibility that individuals with AN might have a DA related disturbance of reward mechanisms contributing to altered hedonics of feeding behavior and their ascetic, anhedonic temperament.*

Key Words: Anorexia nervosa, dopamine, positron emission tomography, [^{11}C]raclopride, eating disorders, brain imaging

Anorexia nervosa (AN) is a disorder of unknown etiology that tends to begin in adolescence in women who develop a relentless desire to lose weight (American Psychiatric Association 2000). Women with AN often have a cluster of stereotypic behaviors that include extremes of food ingestion, anxious and obsessive thoughts, and increased physical activity. Individuals with AN have anhedonic, overcontrolled, perfectionistic personalities (Anderluh et al 2003). They seem to find little that is rewarding in life, aside from losing weight.

Several lines of evidence suggest dopamine (DA) function could contribute to the pathophysiology of AN. Dopamine function contributes to the modulation of motor activity (Alexander et al 1990), weight and feeding behaviors (Halford et al 2004), and reinforcement and reward (Volkow et al 2002). There is some indication that individuals with AN respond to typical and atypical neuroleptics (Brewerton 2004; Cassano et al 2003). Women recovered from restricting type AN (REC AN-R) had a reduction of the DA metabolite homovanillic acid (HVA) in cerebrospinal fluid (CSF) compared with control women (CW) (Kaye et al 1999). Finally, individuals with AN have altered frequency of functional polymorphisms of D2 receptor genes that might affect receptor transcription and translation efficiency (Bergen et al, in press).

This study used positron emission tomography (PET) imaging with the radioligand [^{11}C]raclopride to assess DA D2/D3 receptor function in AN. To avoid the confounding effects of malnutrition on DA activity, women were investigated who had recovered for one or more years from AN. Recent studies suggest that temperament and personality traits occur premorbidly and persist after recovery from AN (Bulik et al 1997; Srinivasagam et al 1995), as do alterations in DA activity (Kaye et al 1999). We hypothesized that REC AN would have reduced intrasynaptic DA in reward-related brain regions such as the antero-ventral striatum (including the nucleus accumbens) and this would be reflected by increased DA receptor binding. Such a disturbance could then suggest a trait disturbance.

Methods and Materials

Ten subjects who were recovered from AN (3 pure restricting-type [AN-R], 1 restricting-purge-type [AN-P], and 6 binge-purge-type AN [AN-BP]) were compared with 12 CW. Subjects were previously treated in the eating disorders treatment program at the Western Psychiatric Institute and Clinic, Pittsburgh, Pennsylvania, or were recruited through advertisements. To be considered "recovered," for at least one year before the study, subjects had to 1) maintain a weight above 85% average body weight (Metropolitan Life Insurance 1983), 2) have regular menstrual cycles, and 3) have not binged, purged, or engaged in significant restrictive eating patterns. Additionally, subjects must not have used psychoactive medication such as antidepressants and not met criteria for alcohol or drug abuse or dependence, major depressive disorder, or severe anxiety disorder within three months of the study. During the ill state, all studied recovered subjects fulfilled criteria for full AN diagnostic criteria (American

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Psychiatric Association 2000). Subjects were interviewed by a psychiatrist who ascertained the absence of pathological eating patterns or other psychopathology. Eating disorder behaviors were assessed with the Eating Disorders Inventory (EDI-2 (Garner 1991), perfectionism with the Multidimensional Perfectionism Scale (Frost et al 1990), and temperament was assessed with the Temperament and Character Inventory (TCI) (Cloninger et al 1994). This study was approved by the University of Pittsburgh Istitutional Review Board, and all subjects gave written informed consent. The PET imaging was performed during the first 10 days of the follicular phase of the menstrual cycle for all subjects. The follicular phase was determined by history. Subjects were admitted to a research laboratory on the eating disorders unit of Western Psychiatric Institute and Clinic at 9:00 PM of the day before the PET study for adaptation to the laboratory and for psychological assessments. The PET study was done the next day. All subjects had the same standardized, monoamine controlled (low protein) breakfast on the morning of the study.

All subjects underwent magnetic resonance (MR) imaging before the PET scan, and MR and PET image data were coregistered as previously described (Frank et al 2002). The PET scans were acquired on an ECAT HR+ PET scanner (CTI PET systems, Knoxville, Tennessee) in three-dimensional mode (63 transaxial planes, 2.4-mm thickness; in-plane resolution = 4.1 mm full-width at half-maximum over a 15.2-cm field of view). Twenty to 25 frames were collected over an acquisition time of 120 min. The PET frames were visually inspected for head motion and a postprocessing correction was performed. The regions of interest (ROIs) were hand drawn (GKF, who was blind to the diagnosis) on the coregistered MR images as described by Drevets et al (2001) and applied to the dynamic PET data to generate time-activity curves. Left and right ROIs were analyzed and then combined. A ROI sampling of the cerebellum was also performed and used as reference region for non-specific binding. We selected the antero-ventral striatum including the nucleus accumbens as primary ROI; however, to test for spill-over effects as well as to conform with convention, the ventral putamen, dorsal caudate nucleus, middle caudate nucleus, and the dorsal putamen were also assessed. We did not expect alterations in those areas. High specific activity [^{11}C]raclopride was used as radio tracer, and methods for synthesis, administration, and blood sampling in our group have been described previously (Drevets et al 2001).

For the imaging data analysis, two methods were applied. First, the Logan graphical method (Logan et al 2001) was used as described previously (Drevets et al 2001). For this method, the binding measure is based upon the ratio of each ROI distribution volume (Dv) value to the cerebellar Dv value (Dv ROI/Dv Cer = DvRatio, DvR) and the binding potential (BP = DvR-1). The Logan method has the advantage of providing information on the cerebellum, wherein the tissue radioactivity concentrations predominantly reflect free and nonspecifically bound radiotracer. The disadvantage is that arterial blood sampling is required during the scanning procedure and this is not always available. We calculated results for the Logan method in all subjects that had arterial blood sampling during the study. If results are robust, the results from the Logan method should be similar to the second method applied, the Reference Tissue Model (Lammertsma and Hume 1996). Here, the [^{11}C]raclopride binding measure is derived from the kinetic rate constant k3/k4, which is equivalent to Dv ratio-1.

A previously validated two-component MR-based partial volume correction algorithm was applied to correct the PET data for the potential dilutional effect of expanded CSF (Meltzer et al 1999), because cerebral volume loss in AN, even after recovery, has been reported (Frank et al 2004).

The SPSS statistical software package (SPSS, Chicago, Illinois) was used for all statistical analyses. Owing to the relatively small sample size, between-group comparisons were made with nonparametric Mann-Whitney U Two-Independent-Samples Tests, calculating two-sided exact significance levels. Correlations were examined with Spearman correlation coefficients. All values are expressed as mean ± SD. As level of significance, a p value of $p < .05$ was selected.

Results

Subject groups were of similar age (CW 27 ± 6 years, REC AN 24 ± 5 years, $p = .2$) and body mass index (CW 23 ± 2, REC AN 22 ± 3, $p = .3$). The mean age of onset of AN was 15 ± 2 years, and REC AN subjects had been recovered for between 12 and 66 months. Compared with CW, REC AN scored higher on EDI-2 drive for thinness-worst ever (REC AN 19.7 ± 2, CW .3 ± 1, $p < .001$) and worst ever Perfectionism (REC AN 108 ± 13, CW 53 ± 11, $p < .001$). Current measures of Harm Avoidance (REC AN 13 ± 9, CW 9 ± 5, $p = .5$), Novelty Seeking (REC AN 22 ± 6, CW 20 ± 5, $p = .4$), and Reward Dependence (REC AN 18 ± 3, CW 19 ± 3, $p = .5$) were similar between groups.

Eight REC AN and eight CW had arterial blood sampling during PET scanning. This method showed increased antero-ventral striatal [^{11}C]raclopride binding in REC AN (2.3 ± .4) compared with CW (1.91 ± .3) ($p = .028$). Other ROIs, including the cerebellum, did not show significant differences between groups. There was a trend, however, toward higher [^{11}C]raclopride binding for REC AN compared with CW in the ventral putamen (CW 2.79 ± .2, REC AN 2.98 ± .3; $p = .1$) and the middle caudate (CW 2.33 ± .11, REC AN 2.56 ± .2; $p = .05$).

The reference tissue model was then applied to the full study sample. The 10 REC AN studied had significantly higher [^{11}C]raclopride binding potential (BP) (Figure 1) than the 12 CW for the antero-ventral striatum (CW 1.98 ± .4, REC AN 2.33 ± .3, $p =$

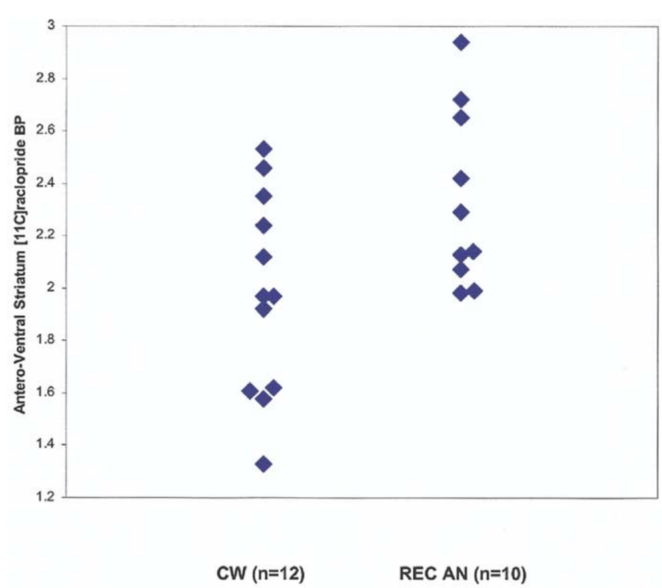

Figure 1. Increased [^{11}C]raclopride binding potential (BP) in the antero-ventral striatum in recovered anorexic women (REC AN) compared with control women (CW).

.036). This suggested a robust finding, and data are presented for this larger sample size. There were no significant group differences in [^{11}C]raclopride BP for the ventral putamen (CW 2.79 ± .3, REC AN 2.97 ± .3, p = .3), dorsal putamen (CW 2.97 ± .4, REC AN 2.78 ± .2, p = .08), middle caudate (CW 2.30 ± .3, REC AN 2.47 ± .2, p = .1), and dorsal caudate (CW 2.47 ± .3, RAN AN 2.26 ± .3, p = .09). Figure 2 shows increased [^{11}C]raclopride binding in an REC AN subject compared with an age matched CW subject.

The injected dose of [^{11}C]raclopride was similar between groups (p = .6), and repeated measures analysis in subjects with arterial blood sampling showed similar metabolites in plasma (p = .23).

Neither age, body mass index, nor length of recovery were correlated with [^{11}C]raclopride binding. Antero-ventral striatal values for REC AN-R tended to be higher compared with REC AN-BP type, but this was statistically not significant, although this is a relatively small sample size with limited power. A lifetime diagnosis of major depression (n = 6) or OCD (n = 5) was not related to [^{11}C]raclopride BP. For REC AN, Harm Avoidance was significantly and positively associated with [^{11}C]raclopride binding in the dorsal caudate (ρ = .9, p = .0004, p = .008 Bonferroni corrected, Figure 3) and dorsal putamen (ρ = .8, p = .004), but not in the antero-ventral striatum (rho = −.3, p = .3).

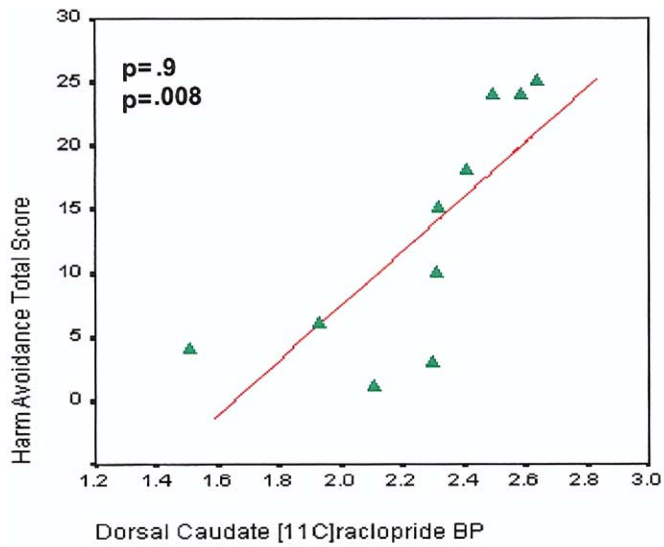

Figure 3. Correlation (Spearman [rho] coefficient) of Harm Avoidance Total Score and Dorsal Caudate [^{11}C]raclopride binding potential (BP) in recovered anorexic subjects; p value Bonferroni corrected.

Discussion

This is the first study to investigate D2/D3 receptors in AN in vivo with PET. A mixed group of REC AN-R and REC AN-BP women had increased [^{11}C]raclopride BP in the antero-ventral striatum. Because PET measures of [^{11}C]raclopride binding are sensitive to endogenous DA concentrations (Drevets et al 2001), this difference could be accounted for either by a reduction in the intrasynaptic DA concentration or by an elevation of the density and/or affinity of the D2/D3 receptors in this region.

People with AN are motorically restless and driven to over-exercise in a manner resembling stereotypy. In animals, drugs that stimulate DA receptors induce hyperactivity and stereotypy, and Parkinson's disease, a degeneration of DA pathways, is associated with reduced motor activity (Maruya et al 2003). A previous study from our group (Kaye et al 1999) found reduced CSF HVA in REC AN-R. That finding lead to the hypothesis of possibly increased postsynaptic DA receptor binding in AN in a negative feedback fashion (Cooper et al 2003). For example, a recent [^{11}C]raclopride imaging study showed reduced plasma HVA and increased D2 binding in response to catecholamine depletion (Verhoeff et al 2003). Moreover, studies in rodents find inverse relationships between DA metabolism and D2 receptor binding (Galkina and Podgornaya 1996). Thus, reduced CSF HVA might be consistent with the results described herein. Whether AN have a compensatory up-regulation of the D2/D3 receptors (Cooper et al 2003) is not known. Motor hyperactivity in AN, however, might be consistent with increased DA neuroreceptor activity.

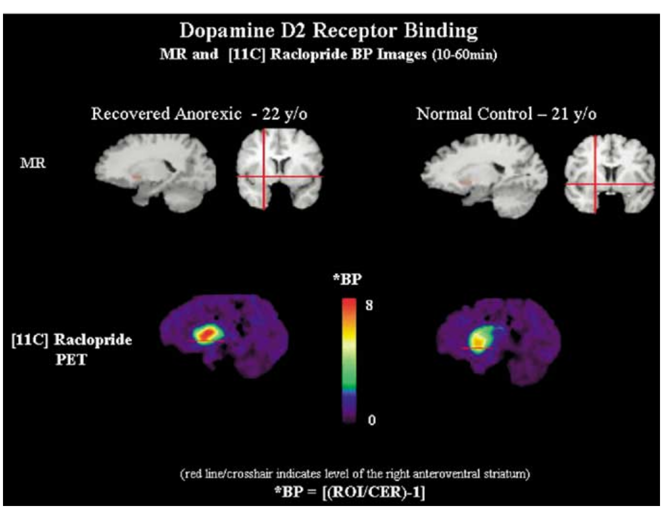

Figure 2. Comparison of one recovered anorexic subject (REC AN) and an age-matched control woman (CW). MR, magnetic resonance; BP, binding potential; PET, positron emission tomography (image); ROI, region of interest; CER, cerebellum.

Another psychiatric disorder, attention-deficit/hyperactivity disorder (ADHD), has been associated with increased D2/D3 receptor binding in a small group of ADHD youth that was related to reduced brain blood perfusion during birth (Lou et al 2004). A more recent study did not find D2/D3 receptor binding differences in adolescents compared with young adults (Jucaite et al 2005), although striatal mean receptor binding was higher in the ADHD group. Attention-deficit/hyperactivity disorder is not associated with a primary disturbance of eating behavior, although individuals with ADHD often respond to stimulants such as methylphenidate, which is relatively selective for DA neurotransmission (Kuczenski and Segal 1997), and loss of appetite might occur as a side effect of this medication.

It is of potential relevance that decreased D2/D3 receptor binding has been found in obese subjects (Wang et al 2004). That finding supports the possibility that D2/D3 receptor binding might be inversely related to weight and eating, with AN on one end, and obesity on the other end of the spectrum. Thus, increased D2/D3 receptor availability in AN might contribute to a drive to become emaciated. It is worth noting that food restriction has been shown to increase D2/D3 receptor activity in rats (Carr et al 2003). Although REC AN subjects continue to have some aberrant meal patterns and tend to still have desires to restrict their food, we do not think food restriction accounts for our findings in AN, because REC AN subjects were at normal weight and had normal blood glucose and ketone bodies (data not shown).

The finding of increased [^{11}C]raclopride BP in the antero-ventral striatum, a region that has been associated with the modulation of reward, reinforcement, and addiction, is intriguing. Neuroimaging studies suggested a role for DA in the pathophysiology of substance abuse and associated craving. For example, some studies show that individuals with drug addictions have reduced D2/D3 receptor binding (Wang et al 2004). Some relationship between addiction and eating disorder has been postulated (Marrazzi et al 1990). In fact, individuals with bulimia nervosa have high rates of substance abuse, whereas AN-R have low rates of substance and alcohol disorders (Bulik et al 2004; Lilenfeld et al 1998). Whether increased D2/D3 receptor availability protects individuals from substance abuse is highly speculative, but this should be investigated in future studies.

Dopamine activity might not directly produce reward, but rather, seems to modulate neuronal activity to "achieve an optimal stimulus response" (Cooper et al 2003) and might help organisms with making appropriate choices (Redgrave et al 1999). Volkow et al (2004) has postulated that decreased DA function in addicted subjects results in decreased sensitivity to non-drug stimuli, including natural reinforcers. We hypothesize that the D2/D3 receptor system is overactive in AN, and thus, might not respond appropriately to salient stimuli. Individuals with AN have long been noted to be anhedonic and ascetic, able to sustain self-denial of food as well as most comforts and pleasures in life. Moreover, ill AN often show ego-syntonic denial and resistance and ignore feedback about their precarious state of health, and it is possible that overactive D2/D3 receptors in the antero-ventral striatum might make anorexic subjects vulnerable to developing the ill state.

No significant relationship between antero-ventral D2/D3 receptor binding and behavior was found in either group. For the REC AN subjects, however, dorsal caudate [^{11}C]raclopride binding was significantly related to Harm Avoidance after correction for multiple comparisons. Although there were not significant differences in Harm Avoidance scores between groups in this small sample, a considerable literature suggests that Harm Avoidance is elevated in individuals who are ill and recovered from AN (Kaye et al 2004; Wagner et al, unpublished data) and is thus a trait-related behavior. Harm Avoidance has been found to correlate with caudate DA activity in Parkinson's disease patients (Kaasinen et al 2001). In addition, striatal DA activity has been linked to trait anxiety in healthy subjects (Laakso et al 2003).

In terms of limitations, this pilot study combined restricting- and binge-purge type REC AN to increase sample size. We had found that reduced CSF HVA only occurred in REC AN-R in the past (Kaye et al 1999). In this small sample, the subtypes were statistically not different, although [^{11}C]raclopride BP for the restricting type subjects tended to be higher than for the binge-purging subjects. This finding, however, could be simply a question of power. Future studies with larger sample sizes will be needed to test the hypothesis that increased D2/D3 BP occurs on a continuum, with REC AN-R having higher values than REC AN-BP, and REC AN-BP having higher values than CW. Thus, it remains to be determined whether there are subgroup differences. In addition, this study cannot address whether the increased receptor binding is due to increased density of the D2/D3 receptors or whether there is increased binding caused by reduced intrasynaptic DA and reduced competition with the radioligand. Future studies are necessary to address this issue. Also, this DA finding in REC AN might suggest that this is a trait-related disturbance; it cannot be excluded, however, that this could also be a persistent scar from the illness, because altered DA activity during critical developmental periods might have persistent effects on DA receptor interactions (Johnson and Bruno 1990). Still, this finding could help explain, in part, treatment resistance in AN.

In conclusion, this study suggests that increased D2/D3 receptor binding occurs in REC AN subjects. This finding might help explain why individuals with AN are able to lose weight, resist eating, overexercise, are protected from substance abuse, and are insensitive to normal rewards.

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