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¹²³I-ADAM SPECT imaging of serotonin transporter binding in patients with night eating syndrome: a preliminary report

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Abstract

Night Eating Syndrome (NES) represents a delay in the circadian pattern of food intake, manifested by evening hyperphagia and/or nocturnal awakenings accompanied by ingestions of food. A neurobiological marker of NES has been implicated with the recently discovered therapeutic response to the selective serotonin reuptake inhibitor (SSRI), sertraline. This pilot SPECT (single photon emission computed tomography) study compared the serotonin transporter (SERT) uptake ratios of night eaters to those of healthy controls. Six night eaters underwent SPECT imaging using the radiopharmaceutical ¹²³I-ADAM. Uptake, compared to that of the cerebellum, was obtained for the midbrain, basal ganglia, and temporal lobes; uptake ratios were compared to those of six healthy controls. Night eaters had significantly greater SERT uptake ratios in the midbrain than healthy controls. These findings, in conjunction with the therapeutic response of NES to sertraline, indicate that the serotonin system is involved in the pathophysiology of NES.

Keywords

serotonin transport; midbrain; circadian; eating behavior

I. Introduction

Night Eating Syndrome (NES) represents a delay in the circadian pattern of food intake, manifested by evening hyperphagia (consuming $\geq 25\%$ of the total daily food intake after the evening meal) and/or nocturnal awakenings accompanied by ingestions of food (O'Reardon et al., 2004). First recognized in 1955, NES is associated with life stress, depressed mood, and morning anorexia (Stunkard et al., 1955). The neurobiology of NES has been advanced with the recently discovered therapeutic response of NES to sertraline (O'Reardon et al., 2004; O'Reardon et al., 2006; Stunkard et al., 2006) and to other selective serotonin reuptake inhibitors (SSRI) (Miyaoka et al., 2003) suggesting that the serotonin system is active in its pathophysiology.

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The extent of serotonin transporter (SERT) binding has been the subject of several studies of psychiatric disorders using single photon emission computed tomography (SPECT) and positron emission tomography (PET). The results of these studies have varied, depending upon the disorder, ligands, and areas of interest (Vaswani et al., 2003).

Studies using SPECT have shown, compared to healthy controls, lower SERT availability in patients diagnosed with bulimia nervosa (Tauscher et al., 2001), binge eating disorder (Kuikka et al., 2001), and seasonal affective disorder (Willeit et al., 2000). Elevated SERT availability has been noted less commonly. Studies of substance dependence have reported increased SERT availability among cocaine dependent patients, both in vivo during acute abstinence (Jacobsen et al., 2000) and post mortem (Mash et al., 2000). One study of obsessive compulsive disorder reported increased midbrain SERT availability (Pogarell et al., 2003), while another reported decreased availability (Stengler-Wenzke et al., 2004). Elevated levels were also the subject of a case report of a patient with Bipolar II (Tolmunen et al., 2004).

SERT binding among patients with major depressive disorder (MDD) has been the subject of conflicting results (Stockmeier, 2003), with studies finding higher SERT binding (Ichimiya et al., 2002), lower SERT binding (Malison et al., 1998; Newberg et al., 2005), or no difference (Meyer et al., 2004; Herold et al., 2006). These discrepant findings are likely due to methodological differences, such as sample size, choice of ligand and region of interest, and variability among patient characteristics.

No study has examined SERT availability among night eaters. The strong response of NES to sertraline (O'Reardon et al., 2004; O'Reardon et al., 2006; Stunkard et al., 2006) suggests that SERT availability among night eaters should be examined. In the present study, SPECT imaging using the SPECT radiopharmaceutical ^{123}I -ADAM (Catafu et al., 2005; Newberg et al., 2005) compared SERT binding in the midbrain, medial temporal region, and the basal ganglia of non-depressed patients with NES and healthy controls.

2. Methods

2.1 Participants and Assessment

Six persons diagnosed with NES were recruited for this study (Mean age = 37.7 ± 11.2 years; Mean BMI = 26.6 ± 2.1 kg/m²; three women; five Caucasian). The diagnosis of NES was established with 7 day food and sleep records kept on an outpatient basis, as well as clinical interview using the Night Eating Syndrome History and Inventory (NESHI; unpublished structured clinical interview). The NESHI included questions about the schedule and amount of food intake throughout the 24-hour day, history of NES symptoms, sleeping routine, mood symptoms and life stressors, weight and diet history, and previous treatment strategies for NES. Patients were diagnosed with NES if they consumed $\geq 25\%$ of total daily calories after dinner and/or experienced nocturnal awakenings with ingestions of food three or more times per week; symptoms had to be present for at least three months prior to interview.

Patients with NES completed the Night Eating Questionnaire (NEQ; Allison et al., in press), which is a 14 item self report measure assessing hunger and craving patterns, percentage of calories ingested after the evening meal, insomnia and awakenings, nocturnal food cravings and ingestions, and mood. Higher NEQ scores (range 0–56) are indicative of greater NES symptomatology. The Beck Depression Inventory (BDI; Beck, 1996), a 21 item self report measure of depressed mood, was used to assess symptoms of depression. Patients scoring 17 or below and who did not currently meet criteria for MDD were eligible for imaging. The mean BDI score for the NES patients was 8 ± 6 points.

Exclusion criteria included: psychotic disorder, bipolar disorder, current substance use disorder, or eating disorder as assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First et al., 1996), diabetes, sleep apnea, night shift work, current participation in a weight loss program, use of psychotropic medications during the past 8 weeks, or any active medical condition that could affect cerebral function.

Two NES patients had previous exposure to SSRI treatment: the patient with the lowest levels of SERT uptake had stopped SSRI treatment eight weeks prior to imaging, and the second patient had SSRI exposure in 1992. None of the NES patients had previous exposure to methylenedioxymethamphetamine (MDMA), and only one was a social smoker.

Six healthy controls were used as a comparison group (Mean age = 36.7 ± 11.2 years; Mean BMI = 23.9 ± 6.4 kg/m²; four female; five Caucasian); these participants' characteristics and screening procedures were previously reported (Newberg et al., 2005). Controls and night eaters did not differ significantly in age, BMI, gender, or ethnicity. None of the controls met lifetime criteria for any Axis I disorder, had an active medical condition, or had used SSRIs within three months of imaging (Newberg et al., 2005). In addition, all controls were non-smokers and MDMA naïve.

For both the NES and control groups, the use of ¹²³I-ADAM required exclusion if the participant had a history of allergic reaction to shellfish or iodine. Women were excluded if they were breastfeeding or if they tested positive for pregnancy within 48 hours prior to ¹²³I-ADAM injection; menstrual status was not assessed.

The study was approved by the Institutional Review Board of the University of Pennsylvania, and all participants provided informed consent for participation. The research was conducted under the Food and Drug Administration Investigational New Drug application 65,542.

2.2 Scanning Procedure and Image Processing and Analysis

The scanning procedure for night eaters was identical to that previously reported by Newberg et al. (2005). Participants were initially given 18 drops of concentrated Lugol's solution to block the thyroid. An intravenous catheter was inserted and capped, and 185 MBq (5 mCi) of ¹²³I-ADAM was administered. After injection of ¹²³I-ADAM, the intravenous catheter was removed. Vital signs and EKG were evaluated from 10 minutes before to 10 minutes after injection in order to assess physiological changes; none were observed. Participants returned four hours after ¹²³I-ADAM administration for a 60-minute brain SPECT scan.

SPECT scans of the brain were acquired on a triple-head gamma camera (3000XP; Picker) equipped with ultra-high-resolution fanbeam collimators, which provide a spatial resolution of 6.7 mm in full width at half maximum at 10 cm. Image reconstruction was performed using filtered-backprojection, with a simple, low pass filter (order 4, cutoff 0.35). Photon attenuation correction was performed using Chang's first order correction method (coefficient of 0.11 cm⁻¹). The acquisition parameters include a continuous mode with 40 projection angles over a 120° arc to obtain data in a 128 × 128 matrix with a pixel width of 2.11 mm and a slice thickness of 3.56 mm with a center of rotation of approximately 14 cm.

All SPECT images were realigned and resliced using an oblique reformatting program. Thus, all regions were analyzed in the same orientation. Regions of interest (ROIs), based on a previously described template (Resnick et al., 1993), were placed on the transaxial images on the midbrain, medial temporal region and basal ganglia (Newberg et al., 2005). The regions of interest were initially based upon anatomical MR images, and were transposed onto each of the SPECT scans. The template with labeled regions of interest is presented in Figure 1. Similar

regions have been used in other papers recently reported in the literature (Catafu et al., 2006; Kline et al., 2006; Lin et al., 2006).

2.3 Statistical Analysis

The SERT uptake ratio (ROI compared to the cerebellum) at 4–5 hours after administration of ^{123}I -ADAM was the primary outcome measure. Previous studies have demonstrated that a comparison of the regions to the reference region of the cerebellum allow for adequate quantitation of SERT binding, comparable to full kinetic analysis (Acton et al., 2001; Newberg et al., 2005).

Because the cerebellum does not have SERTs, these values, therefore, represent non-specific binding. When evaluated at 4–5 hours, it reflects a pseudoequilibrium phase in which the ratio of specific ROIs to the reference region results in a semiquantitative value that is comparable to the full kinetic analysis (Acton et al., 2001; Newberg et al., 2005). Of note, the mean cerebellar uptake value was 368 ± 77 counts per pixel for controls and 476 ± 47 counts per pixel for night eaters ($t_{(1,10)} = 2.9$; $p = 0.007$), reflecting differences in the injection amount and scan conditions. These differences were equalized by dividing the uptake in the actual region of interest by the cerebellum, and statistically analyzing the ratio of the two.

Analysis of covariance (ANCOVA) controlling for age, gender, and ethnicity was used to compare ^{123}I -ADAM uptake ratios in the ROIs (midbrain, medial temporal lobes, and basal ganglia) of the night eaters and healthy controls.

3. Results

The results of ADAM scans for NES patients compared to healthy controls are presented in the Table 1; uptake values represent the region:cerebellum ratios.

Patients with NES had significantly increased uptake in the midbrain compared to controls ($F_{(1,7)} = 23.7$, $P < 0.01$); age was the only significant covariate ($F_{(1,7)} = 6.1$, $P = 0.04$), with older age associated with less SERT availability. Night eaters had higher adjusted mean values than controls in the left and right temporal lobes, although they did not achieve statistical significance. No differences were noted in the basal ganglia.

Figure 2 shows the variability in midbrain:cerebellum SERT uptake ratios for the patients with NES and the healthy controls. Figure 3a and 3b provides an example of midbrain SERT uptake for both groups.

4. Discussion

This is the first study examining SERT uptake in patients with NES. The impetus for this investigation was the efficacy of the SSRI, sertraline, in the treatment of NES in three clinical trials (O'Reardon et al., 2004; O'Reardon et al., 2006; Stunkard et al., 2006). This efficacy suggests that the serotonin system is involved in the pathophysiology of this syndrome.

The current study showed that night eaters, compared to controls, had significantly greater midbrain SERT binding, with a large effect size of 0.77. Left and right temporal lobe differences were noted, but did not reach statistical significance, possibly due to the small sample size.

How is increased SERT binding related to the response of NES to sertraline? These findings may reflect a syndrome-specific increase in SERT that results in an overall decrease of serotonin within the synapse. Thus, sertraline may act by blocking the homeostasis.

It is intriguing that SERT availability among night eaters is different from that which has been found for persons with bulimia nervosa (Tauscher et al., 2001) and binge eating disorder (Kuikka et al., 2001). These findings may reflect differences in eating pathology manifested by the binge eating behavior of persons with bulimia nervosa and binge eating disorder versus the appropriately portioned, but circadian-delayed eating behavior of night eaters (Allison et al, 2005).

NES appears to have little in common with the few psychiatric conditions with elevated SERT binding: chronic cocaine dependence, one study of obsessive compulsive disorder, and bipolar II disorder. Night eaters are more likely to have a history of substance abuse and dependence than non-night eaters (Lundgren et al., 2006), although this is not specific to cocaine use. No studies to date have linked night eating behavior to obsessive compulsive disorder or mania.

The main limitation of this report is the small sample size which may have impacted the statistical power necessary to detect differences in the temporal lobes. The pilot nature of this study required this limitation, but does not negate the importance of these findings. Future studies should expand the study of SERT binding in night eaters to determine if levels of SERT binding can predict SSRI treatment response. SERT availability should also be examined in subgroups of night eaters (e.g., depressed versus non-depressed, early versus late onset, and familial versus non-familial) to determine if difference in SERT binding are a function of additional variables.

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Figure 1.

Figure shows template with labeled regions of interest. Rt BG = right basal ganglia; Lt BG = left basal ganglia; MB = midbrain; Rt Temp = right temporal lobe; Lt Temp = left temporal lobe; Rt Cer = right cerebellum; Lt Cer = left cerebellum.

Figure 2.

Figure shows individual data points of midbrain:cerebellum SERT uptake ratios for controls and night eaters. Night eaters show significantly higher levels of midbrain SERT uptake compared to control subjects. Circles represent females and diamonds represent males.

Figure 3a.

Figure 3b.

Figure 3.

Figure 3a and 3b. Figure 3a shows ADAM SPECT scans of controls. The arrow points to the midbrain. Figure 3b shows ADAM SPECT scans of patients with Night Eating Syndrome. The arrow points to the midbrain.

Table 1

Comparison of SERT uptake ratios between persons with NES and healthy controls controlling for age, gender, and ethnicity.

Region of Interest	NES (<i>n</i> = 6) <i>M</i> ± <i>SD</i>	Control (<i>n</i> = 6) <i>M</i> ± <i>SD</i>	Statistic and Significance	Partial Eta Squared
Right Temporal Lobe	1.47 ± 0.09	1.36 ± 0.09	$F_{(1,7)} = 3.9, P = 0.09$	0.36
Left Temporal Lobe	1.46 ± 0.11	1.32 ± 0.11	$F_{(1,7)} = 3.5, P = 0.10$	0.34
Midbrain*	2.24 ± 0.11	1.90 ± 0.11	$F_{(1,7)} = 23.7, P < 0.01$	0.77
Right Basal Ganglia	1.20 ± 0.11	1.17 ± 0.11	$F_{(1,7)} = 0.10, P = 0.76$	0.01
Left Basal Ganglia	1.18 ± 0.16	1.17 ± 0.16	$F_{(1,7)} = 0.03, P = 0.87$	0.00

Note. Means adjusted for age, gender, and ethnicity.

* Age was a significant covariate, $P = 0.04$; older age associated with decreased SERT binding.