NeuroImage 86 (2014) 306–310

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Decreased norepinephrine transporter availability in obesity: Positron Emission Tomography imaging with (S,S)-[^{11}C]O-methylreboxetine

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ARTICLE INFO

Article history:
Accepted 1 October 2013
Available online 10 October 2013

Keywords:
[^{11}C]-MRB
Norepinephrine
PET
Human
Obesity
BMI

ABSTRACT

Objectives: Noradrenergic dysfunction is implicated in obesity. The norepinephrine transporter (NET) regulates the synaptic availability of norepinephrine. However, NET availability has not been previously characterized in vivo in obese people using Positron Emission Tomography (PET) imaging. Here we report findings evaluating NET availability in individuals with obesity and matched lean (i.e., normal weight) comparison subjects.
Methods: Seventeen obese but otherwise healthy individuals with a mean ± SD body mass index (BMI) of 34.7 ± 2.6 and 17 lean individuals with a mean ± SD BMI of 23.1 ± 1.4 were studied using a high-resolution research tomograph (HRRT) and (S,S)-[^{11}C]O-methylreboxetine ([^{11}C]-MRB), a radioligand selective for the NET. The regional brain NET binding potential (BP_{ND}) was estimated by the multilinear reference tissue model 2 (MRTM2) with the occipital cortex as a reference region. BP_{ND} for regions of interest were obtained with the Automated Anatomic Labeling (AAL) template registered to individual's structural MR scans.
Results: Obese individuals had lower NET BP_{ND} values in the thalamus ($p < 0.038$, 27% reduction) including within the pulvinar ($p < 0.083$, 30% reduction), but not in the hypothalamus, locus coeruleus or the raphe nuclei, compared to lean individuals. When age was included as a covariate, the difference in NET BP_{ND} values remained significant in the thalamus ($p < 0.025$) and pulvinar ($p < 0.042$).
Conclusions: These results indicate that NET availability is decreased in the thalamus, including the pulvinar, in obese individuals. These findings further support data indicating noradrenergic dysfunction in obesity and suggest impaired NE clearance in obesity.

Introduction

Obese individuals suffer adverse health effects including hypertension and Type-2 diabetes (Landsberg et al., 2013). The cost of obesity to society is tremendous due to illnesses associated with obesity and losses in productivity at work (Thorpe and Philyaw, 2012). In the United States, 36% of adults and 17% of children are obese according to the Centers for Disease Control and Prevention (Flegal et al., 2012; Ogden et al., 2012). As prevalence estimates have been rising over time, understanding the biological factors underlying obesity could help advance prevention and treatment efforts.

While catecholaminergic dysfunction in obesity has largely focused on dopamine (Frascella et al., 2010; Kenny, 2011; Volkow et al., 2013; Wang et al., 2001), data also support noradrenergic contributions (Carlsson, 1979). Inhibition of either α1- or β2-noradrenergic receptors in the ventromedial/paraventricular hypothalamus reduces endogenous levels of norepinephrine (NE), decreasing food intake, while activation of α2-noradrenergic receptors of the lateral hypothalamus increases NE, increasing food intake (Bays and Dujovne, 2002; Levin, 1995, 1996). In people, intake of highly caloric diets increases noradrenergic turnover in peripheral tissues, leading to elevated resting plasma norepinephrine levels that may underlie increased excretion of norepinephrine and elevated rates of hypertension in obese versus lean people (Kotsis et al.,

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http://dx.doi.org/10.1016/j.neuroimage.2013.10.004

2010; Lee et al., 2001). These findings suggest an important role for the noradrenergic system in eating behaviors, obesity and obesity-related health conditions.

The concentration of NE at noradrenergic synapses is regulated by reuptake via the norepinephrine transporter (NET). The NET is expressed centrally in cortical and subcortical regions including the locus coeruleus, thalamus, hypothalamus, and hippocampus (Ding et al., 2010; Schroeter et al., 2000). Given their expression in brain regions proposed to underlie motivated behaviors (Chambers et al., 2003), NETs may contribute importantly to motivated behaviors underlying overeating in obesity. Additionally, the NET is targeted by therapeutic and abused drugs including stimulants and certain antidepressants (Gallezot et al., 2011; Hannestad et al., 2010), some of which may alter appetite and over time body mass, suggesting that the NET may represent an important target for medication development (Zhou, 2004).

We have previously demonstrated that the radioligand (S,S)-[^{11}C]O-methylreboxetine ([^{11}C]MRB) binds to the NET in the brain with higher specific binding and lower variability in non-specific binding than previous NET radioligands (Ding et al., 2005, 2006). This tracer has been employed successfully to assess occupancy of NET in clinical and preclinical studies (Gallezot et al., 2011; Hannestad et al., 2010) as well as to assess NET availability changes in cocaine-dependent individuals (Ding et al., 2010). To investigate NET availability in obesity, we compared [^{11}C]MRB binding potential values in seventeen obese and seventeen lean individuals, hypothesizing that we would observe between-group differences regions with high [^{11}C]MRB binding from our earlier work, including the thalamus, hypothalamus, locus coeruleus, and the raphe nuclei (Ding et al., 2010; Gallezot et al., 2011; Hannestad et al., 2010).

Materials and methods

Subjects

Thirty-four adults, including 17 obese (9 males, 32.1 ± 10.2 years of age) and 17 age- and gender-matched lean (9 males; 33.7 ± 11.5 years) individuals, participated in this study. The two groups differed both in weight (105.2 ± 12.7 vs. 66.7 ± 9.0 kg; $p < 0.0001$) and BMI scores (34.7 ± 2.6 vs. 23.1 ± 1.4; $p < 0.0001$). All participants were screened to be free of major medical illness including past or present neurological and Axis-I psychiatric (First et al., 1995) conditions, denied current or past illicit substance use, and showed negative urine toxicology tests for stimulants, opioids, marijuana, and benzodiazepines at the time of the PET study. Participants were further required to be free of MRI contraindications based on the safety guidelines of Yale's Magnetic Resonance Research Center. All participants signed a written consent according to a protocol approved by the Yale Human Investigation Committee and the Yale-New Haven Hospital Radiation Safety Committee.

Magnetic resonance (MR) imaging

Participants were scanned on a Siemens 3-Tesla scanner (Trio; Siemens AG, Erlangen, Germany). Data for each participant consisted of a single high-resolution T1-weighted gradient-echo scan: 176 slices; 1 mm^3 isotropic voxels; field of view = 256 × 256 mm; data acquisition matrix = 256 × 256; TR = 2530 ms; TE = 3.66 ms, bandwidth = 181 Hz/pixel; flip angle = 7. The MR images were used for registration to an atlas to define regions of interest (ROIs).

Positron Emission Tomography (PET) imaging

The (S,S) enantiomer of the methyl analog of reboxetine, 2-[alpha-(2-methoxyphenoxy)benzyl] morpholine was radiolabeled with carbon-11 ([^{11}C]MRB), as previously described (Ding et al., 2003). Subjects were scanned at the Yale PET Center on the High-Resolution Research Tomograph (HRRT) scanner. A 6-minute transmission scan was acquired using an orbiting ^{137}Cs point source prior to radiotracer injection for attenuation correction. One venous catheter was established in the forearm for a bolus injection of [^{11}C]MRB. A dose of 596 ± 150 MBq [^{11}C]MRB with mass per weight of 0.024 ± 0.017 μg/kg and specific activity of 124 ± 67 MBq/nmol was delivered as a 2-minute bolus and the total scan time was 120 min. The acquisition of HRRT list-mode data began just prior to the initiation of the bolus injection delivered through a syringe pump (Harvard PHD 22/2000, Harvard Apparatus, Holliston, Massachusetts, United States). All scanning took place with the subjects in supine position and with an optical motion-tracking tool fastened to the subject's head (Vicra, NDI systems, Waterloo, Canada) via a swim cap.

The list mode data were reframed into a dynamic sequence of: 6 × 30 s, 3 × 1 min, 2 × 2 min, 22 × 5 min. Dynamic images (207 slices and pixel size = 2 × 2 mm^2) were reconstructed using ordered subset expectation maximization (OSEM, 2 iterations and 30 subsets) with corrections for measured attenuation, normalization, scatter, randoms, dead time, and event-by-event motion using the Motion-compensation OSEM List-mode Algorithm for Resolution-recovery Reconstruction (MOLAR) algorithm as previously described (Carson et al., 2003).

Image analyses

For registration, a summed PET image (0–10 min) was used for coregistration to the individual subject's MRI, which was linearly coregistered to a template MRI to determine the ROIs identified using The Automated Anatomical Labeling template (Tzourio-Mazoyer et al., 2002). The transformation was estimated based on normalized mutual information (FLIRT, http://www.fmrib.ox.ac.uk/analysis/research/flirt/). Regional [^{11}C]MRB uptake was quantified as binding potential (BP_{ND}), which is proportional to the density of available transporters for binding (Innis et al., 2007). The occipital cortex was used as a reference region as previously described (Hannestad et al., 2010). The estimates of BP_{ND} were obtained using the multilinear reference tissue model 2 (MRTM2; Ichise et al., 2003) that produces parametric BP_{ND} images, with the assumption that the nondisplaceable binding in the occipital cortex and target regions is similar.

We compared BP_{ND} values in the obese and lean groups using a two-tailed two-sample test for each of the regions of interest. Because age has been shown to influence [^{11}C]MRB binding (Ding et al., 2010), we also performed group comparison in a covariance analysis accounting for the differences in age between groups.

Results

The obese and lean individuals did not differ with regard to injected dose (578 ± 154 vs. 614 ± 148 MBq, $p = 0.49$, two-tailed 2-sample t test) or injected mass per kg body weight (0.025 ± 0.019 vs. 0.024 ± 0.015 μg/kg; $p = 0.86$).

NET binding potential (BP_{ND})

Consistent with our earlier studies, high uptake of [^{11}C]MRB was observed in regions rich in NET expression, including the thalamus, hypothalamus and the locus coeruleus and raphe nuclei in the midbrain (Ding et al., 2010). NET BP_{ND} estimates for obese and lean subjects are presented in Fig. 1. Compared to lean participants, obese individuals had significantly lower NET BP_{ND} values in the thalamus (0.31 ± 0.14 vs. 0.43 ± 0.17; $p < 0.038$) and had lower NET BP_{ND} values in the pulvinar approaching significance (0.29 ± 0.19 vs. 0.41 ± 0.22; $p < 0.083$), but not in the hypothalamus, locus coeruleus or the raphe nuclei. Because NET availability decreased with age (Ding et al., 2010) and we found an age effect that was significant for the pulvinar ($p < 0.02$) and at trend level for the thalamus ($p < 0.10$), we accounted for the effects of age in

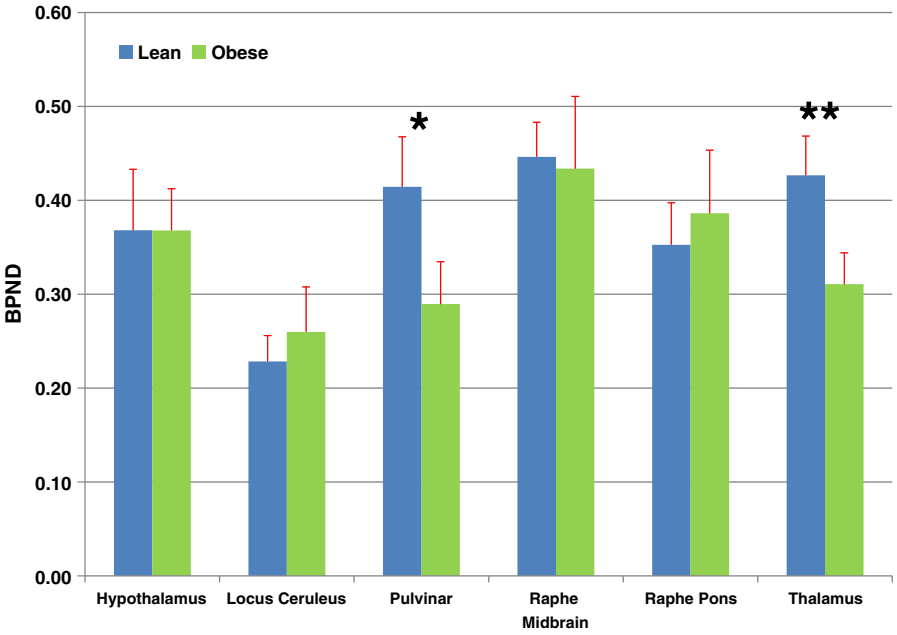

Fig. 1. Norepinephrine transporter binding potential (BP_{ND}) estimates for regions of interest in lean (blue) and obese (green) participants. Histograms showed BP_{ND} in mean ± standard error. Compared to lean participants, obese participants demonstrated decreased BP_{ND} values in the thalamus (**$p < 0.038$) and pulvinar (*$p < 0.083$).

a follow-up covariance analysis. The results showed that the difference in NET BP_{ND} values remained significant in the thalamus ($p < 0.025$) and reached significance in the pulvinar ($p < 0.042$). The other regions remained indistinguishable in NET BP_{ND} between groups. Fig. 2 shows parametric images of a representative participant each from the obese and lean groups.

Since most of the ROIs evaluated in our study are small structures, we considered potential biases in BP_{ND} estimates that may relate to the linear coregistration method used in delineating the ROIs. Thus, we reanalyzed the data using a nonlinear registration approach using the Bioimagesuite software (http://www.bioimagesuite.org/). The use of nonlinear transforms produced minor changes in the results. Compared to lean participants, obese individuals had significantly lower NET BP_{ND} values in the pulvinar (0.13 vs. 0.26; $p < 0.030$). The differences in thalamus were at trend level (0.20 vs. 0.29; $p < 0.067$). The other regions showed no significant differences in NET BP_{ND} between groups. With age correction, pulvinar and thalamus differences became more significant ($p < 0.024$ and 0.052, respectively).

Discussion

Our findings partially confirmed our hypothesis that regional NET availability would differ between obese and lean individuals. Compared to lean people, obese people showed decreased NET binding potential in the thalamus and its pulvinar component after adjusting for age. However, differences in other regions were not observed. The thalamic and pulvinar results are consistent with earlier studies implicating noradrenergic dysfunction in maladaptive feeding and obesity, as discussed earlier. To our knowledge, this is the first in vivo imaging study of NET in obesity and the results directly demonstrate differences in NET availability related to obesity.

The thalamus, including its pulvinar component, have been described as relay stations in motivational neurocircuitry (Chambers et al., 2003; Saalmann et al., 2012) and have been implicated in eating behaviors and obesity. For example, the thalamus becomes activated during pictures of high- versus low-calorie foods (Killgore et al., 2003). Glucose ingestion reduces cerebral blood flow in the hypothalamus and increases functional connectivity between the hypothalamus and thalamus, suggesting a role for these subcortical structures in regulating satiety and eating (Page et al., 2013). Restricted sleep increases cerebral responses to food cues in association with increased activity in the insula, striatum, thalamus, and prefrontal cortices (St-Onge et al., 2012). In obese but not lean individuals, food craving and insulin levels correlated positively with corticolimbic-striatal (including thalamic) activations during exposure to favorite-food and stress cues (Jastreboff et al., 2013). Furthermore, the relationship between insulin resistance and food craving in obese but not lean individuals was mediated by thalamic activation during exposure to favorite-food cues (Jastreboff et al., 2013). In an fMRI study of obese cancer survivors, behavioral lifestyle intervention decreased activation to high-calorie versus non-food cues in regions of reward and motivation circuitry, including the thalamus (Nock et al., 2012). Together, these studies suggest that the thalamus is involved in responses to food cues and intake that are altered in obese individuals and may contribute to excessive eating and obesity.

The current results contrast with those seen in cocaine dependence in which relatively increased [^{11}C]MRB was observed in the thalamus and its pulvinar component (Ding et al., 2010). While it is tempting to speculate that NE systems might regulate eating behaviors differently in cocaine dependence and obesity, future studies are needed to directly examine the roles of noradrenergic function with respect to specific aspects of each condition.

The present findings may also have implications for treatment development for obesity. For example, stimulant medications that target the NET and other biogenic aminergic transporters may reduce appetite and lead to weight loss, and the extent to which these effects might be mediated through thalamic mechanisms and modulated by other therapeutic drugs warrants consideration. Additionally, noradrenergic mechanisms have been implicated in obesity-related medical conditions like hypertension, and the extent to which the current findings might relate to hypertension in obesity deserve examination. Obesity is associated with mental-health disorders (Desai et al., 2009). As drugs targeting the NET have been shown to have efficacy in treating such conditions (e.g., depression), the current findings suggest possible mechanisms relating to their co-occurrence and a possible treatment target for medication development, although additional direct research is needed to explore this possibility.

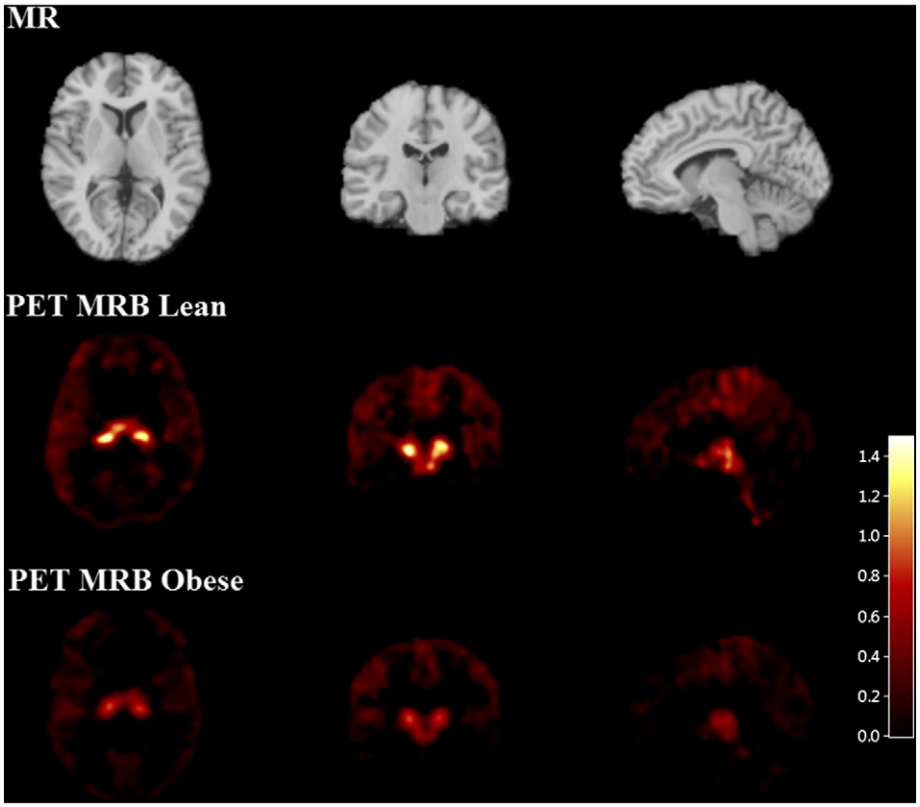

Fig. 2. Images of ^{11}C]MRB BP_{ND} of a representative participant each from the lean and obese groups, with reference to a structural image in axial, coronal, and sagittal sections. [^{11}C]MRB binding is concentrated in the thalamus and midbrain. Compared to the lean participant, the obese participant showed decreased ^{11}]MRB binding.

For PET neuroreceptor/transporter imaging, a binding potential (BP_{ND}) in the range of 1–3, or higher, is desirable. [^{11}C]MRB, with its low binding potential due, in part, to the low concentration of NET, is currently the best available NET PET ligand. We have used [^{11}C]MRB successfully for multiple clinical and preclinical studies (Ding et al., 2010; Gallezot et al., 2011; Hannestad et al., 2010). It is important to note that, with low BP_{ND} values, between-group differences could be artificially introduced if there are between-group differences in the level of nondisplaceable binding, here obtained from the occipital cortex. However, such a bias would affect all regional values. Since the obesity effects were regionally specific (Fig. 1), we cannot ascribe this difference to a between-group difference in nondisplaceable binding, although such group differences may have affected the magnitude and regional distribution of NET differences.

The current study has limitations. For example, although large for a PET study, the sample size is relatively small. Future studies employing larger samples might reveal important individual differences (e.g., gender) that have been linked to important aspects of eating behaviors and obesity. This is particularly important in light of a recent multi-center study that failed to replicate an association between BMI and dopamine transporter binding potential in the dorsal striatum (van de Giessen et al., 2013). Nonetheless, the groups are well matched on important characteristics, including gender and age, lending support to the potential generalizability of the findings. Second, we did not observe a difference in the hypothalamus, which has been implicated in noradrenergic dysfunction in association with obesity. The absence of a significant between-group in NET availability in the hypothalamus should be considered cautiously in that multiple factors (e.g., the small volume of the hypothalamus and the relatively low binding potential of [^{11}C]MRB) may preclude the identification of a significant between-group difference. Although [^{11}C]MRB is currently the most promising NET ligand available, future studies with PET ligands with improved affinity and specificity for the NET and involving larger numbers of subjects may help examine more definitively a role for noradrenergic function in the hypothalamus and other subnuclei of the thalamus in obesity.

In conclusion, we showed that the NET availability in the thalamus and pulvinar is decreased in obese, compared to lean, individuals. These results may provide a useful platform upon which to further investigate noradrenergic functions in obesity.

Acknowledgments

This study was supported by NIH grants UL1-DE019586 and PL1-DA024859, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the National Institute on Drug Abuse (NIDA) through the following awards: RAA017540B and RAA017540Y (American Reinvestment and Recovery Act of 2009), RL1AA017539, R21DA026998, and K02DA026990. The NIH had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Conflict of interest

The authors report no conflicts of interest with the content of this manuscript. Dr. Potenza has received financial support or compensation for the following: Dr. Potenza has consulted for and advised Somaxon, Boehringer Ingelheim, Lundbeck and Ironwood Pharmaceuticals; has had financial interests in Somaxon; has received research support from the National Institutes of Health, Veteran's Administration, Mohegan Sun Casino, the National Center for Responsible Gaming and its affiliated Institute for Research on Gambling Disorders, Glaxo-SmithKline, Psyadon and Forest Laboratories pharmaceuticals; has participated in surveys, mailings or telephone consultations related to drug addiction, impulse control disorders or other health topics; has consulted for gambling and legal entities on issues related to addictions or impulse control disorders;

has provided clinical care in the Connecticut Department of Mental Health and Addiction Services Problem Gambling Services Program; has performed grant reviews for the National Institutes of Health and other agencies; has guest-edited journal sections; has given academic lectures in grand rounds, CME events and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts.

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