Brain, nutrition and metabolism

Studies in lean, obese and insulin resistant humans

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Serotonin transporter binding in the diencephalon is reduced in insulin resistant obese humans
Abstract

Background
Altered brain dopaminergic and serotonergic pathways have been shown in obese rodents and humans, but it is unknown whether this is related to obesity per se or to the metabolic derangements associated with obesity.

Methods
We performed a case-control study in insulin sensitive obese (ISO) and insulin resistant obese (IRO) subjects (n=12) and age-matched lean controls (n=8) and measured serotonin transporter (SERT) binding in the whole diencephalon and specifically in the hypothalamus, as well as dopamine transporter (DAT) binding in the striatum using $^{123}$I-FP-CIT single photon emission computed tomography (SPECT). We assessed insulin sensitivity using the HOMA-IR.

Results
BMI did not differ between the IRO and ISO subjects. SERT binding in the diencephalon was significantly lower in IRO vs ISO subjects but was not different between lean and obese subjects. SERT binding in the hypothalamus tended to be reduced in obese vs lean subjects, but was not different between IRO and ISO subjects. Striatal DAT binding was similar between lean and obese subjects as well as between ISO and IRO subjects.

Conclusions
We conclude that SERT binding in the diencephalon is reduced in insulin resistant subjects independently of body weight while hypothalamic SERT binding tends to be lower in obesity with no difference between insulin resistant and insulin sensitive subjects. This suggests that the metabolic perturbations associated with obesity independently affect SERT binding within the diencephalon.
Introduction

Serotonin is a monoamine neurotransmitter involved in the regulation of food intake and body weight (1), and in rodent studies altered brain serotonergic pathways have been linked to obesity. Neurochemical serotonin depletion in the rodent brain results in obesity and hyperphagia (2) and inversely, infusion of serotonin into the hypothalamus decreases body weight in Zucker rats (3). Pharmacological studies in humans also point towards a role for the serotonin system in body weight regulation (4) since lorcaserin, a serotonin-2C receptor agonist, induces weight loss (5) and short-term use of selective serotonin reuptake inhibitors (SSRIs), which inhibit reuptake of serotonin via the serotonin transporter (SERT), also reduces body weight (4). This suggests that in humans an increase in serotonergic signalling may be favourable for body weight management. In line, SERT binding in subcortical regions (caudate-putamen-thalamus) is inversely associated with BMI (6) and we recently showed reduced SERT immunostaining in the hypothalamic infundibular nucleus in post-mortem tissue of overweight subjects (7). Moreover, in the cerebrospinal fluid of obese women serotonin and its metabolites were lower compared to lean controls (8). Additionally, several studies point towards a regulatory role for central serotonergic signalling in glucose metabolism. Mice lacking the serotonin-2C receptor in proopiomelanocortin (POMC) neurons have normal body weight but exhibit hyperglycemia, hyperinsulinemia, and insulin resistance (9) and SERT deficient mice are hyperglycemic and hyperinsulinemic and have reduced insulin signalling in liver prior to the occurrence of obesity (10). In non-diabetic individuals, short-term treatment with SSRIs decreases fasting blood glucose levels (11) and SERT polymorphisms are linked to the occurrence of diabetes (12). Together these studies suggest a link between serotonergic signalling and body weight regulation as well as a body weight independent effect on glucose metabolism.

In addition to the diencephalic serotonergic system, striatal dopamine has been associated with body weight and glucose metabolism. Obese subjects have lower striatal dopamine D2/3 receptor (D2/3R) binding availability (13) and striatal D2/3R binding is associated with insulin sensitivity (14). Additionally, D2R knockout mice have a blunted insulin response and are glucose intolerant (15). Increasing dopaminergic signaling using the dopamine receptor agonist bromocriptine in rodents and humans improves glucose metabolism (16, 17), and in obese rodents this is accompanied by an increase in striatal dopamine transporter (DAT) expression (18). We hypothesized that cerebral SERT and DAT binding is lower in obese subjects compared to matched lean, healthy controls and that both SERT and DAT binding is associated with glucose homeostasis. To study this, we performed ¹²³I-FP-CIT SPECT to assess SERT binding in the diencephalon with emphasis on the hypothalamus, and DAT binding in the striatum in lean as well as in obese insulin resistant and obese insulin sensitive humans.
Methods

Subjects
We included twelve obese subjects (10 women and 2 men; mean age: 31.7±8.9 years; mean BMI: 36.6±4.4 kg/m²) and 8 age-matched lean controls (all female, mean age: 30.9±10.5 years; mean BMI: 21.3±1.3 kg/m²). All women were premenopausal and measurements were performed in the follicular phase of the menstrual cycle. Participants were in self-reported good health, had normal liver, renal, and thyroid function, did not smoke and did not use any medication. In addition, all subjects had a self-reported stable weight during 3 months prior to inclusion. A 75 g glucose tolerance test was performed to exclude undiagnosed diabetes (19). Substance abusers, shift workers, and subjects with a history of psychiatric or eating disorders (e.g. binge eating, restraint eating) were excluded, as were pregnant women. A pregnancy test was performed upon inclusion. The study protocol was approved by the institutional review board of the Academic Medical Center of the University of Amsterdam and conducted according to the Declaration of Helsinki of October 2008. Written informed consent was received from all participants after explanation of the nature of the study.

Imaging of the serotonin transporter (SERT) and dopamine transporter (DAT)
Each participant underwent single photon emission computed tomography (SPECT) imaging with the radioligand $^{123}$I-FP-CIT (DaTSCAN). A total dose of 115 MBq (range: 110-120 MBq; specific activity > 750 MBq/nmol; radiochemical purity > 98%, produced according to GMP criteria at GE Healthcare, Eindhoven, The Netherlands) was administered intravenously. This tracer can be used to image striatal DAT and extrastriatal SERT binding. SERT and DAT binding can be visualized and quantified adequately in the diencephalon ((hypo)thalamic region) and striatum at 2 and 3 hours after bolus injection respectively, as described previously (20). Participants were scanned at 10:30 AM (i.e. 2 h after injection of the radiotracers) and at 11:30 AM (3 h post-injection) after an overnight fast. Each participant was pre-treated with potassium iodide to block thyroid uptake of free radioactive iodide. SPECT imaging was performed using a 12-detector, single slice brain-dedicated scanner (Neurofocus, 810, Strichman Medical Equipment, Cleveland, OH, USA) using an acquisition protocol as described previously with slight modifications (interslice distance: 5 mm; acquisition time: 210 sec/slice) (20). All scans were reconstructed in 3D mode and corrected for attenuation.

Magnetic Resonance Imaging
A T1-weighted MRI scan of the brain was performed on each individual for anatomical reference on a 3.0T Philips Interna scanner (Philips Healthcare, Best, The Netherlands) with a standard head coil.
**Image analysis**

In the first analysis, a region-of-interest (ROI) analysis was performed to determine specific binding in the striatum, the whole diencephalon (which includes the thalamus, the subthalamus, the hypothalamus, and the epithalamus) and the hypothalamus. A ROI analysis using fixed ROIs was performed by one well-trained researcher (KK) as described previously (21). Briefly, the 4 consecutive slices with the highest binding were selected to assess binding to DAT (3 h post-injection) and SERT (2 h post-injection). Activity in the cerebellum (3 consecutive slices) was assumed to represent non-displaceable binding (nonspecific binding and free radioactivity). A specific-to-nonspecific binding ratio (SNS-BR) was calculated as \((\text{ROI-binding minus cerebellar binding}) / \text{cerebellar binding}\), which was used as the outcome measure (binding potential \((\text{BP}_{\text{ND}})\)). Representative scans with high and low diencephalic SERT binding are shown in Figure 1A and 1B.

In a second analysis, SERT binding in the hypothalamus was assessed using manually drawn ROI on individual MRIs as described previously (22). We used these manually drawn ROIs, as it is not possible to identify the hypothalamus on SPECT images because of the limited spatial resolution. Consequently, ROIs for the hypothalamus and cerebellum were manually drawn on the T1 weighted MRI from each subject using self-developed software (23) (an example is shown in Figure 1C-H.) MRI data were missing from 1 lean and 1 insulin resistant obese (IRO) female subject due to technical problems. The SPECT scan and individual T1 weighted MRI scan were matched in all three \((x,y,z)\) planes for each subject by using the same software. The accuracy of registration was improved by comparing (triangulation) co-registration of the T1 weighted MRI scan with the individual SPECT scans acquired at both time points respectively. The individual T1 weighted MRI scan was registered to both SPECT scans to validate consistency and estimate the registration uncertainty. After matching, the mean amount of radioactivity/ voxel in the hypothalamus was determined and activity in the cerebellum (excluding vermis) was used to represent non-specific binding. Finally, similar to the first analysis, a SNS-BR was calculated as \((\text{hypothalamic binding minus cerebellar-binding}) / \text{cerebellar-binding}\).
Laboratory analysis

Plasma glucose concentrations were measured with the glucose oxidase method using a Biosen C-line plus glucose analyzer (EKF Diagnostics, Barleben/Magedeburg, Germany). Insulin and cortisol were both measured on an IMMULITE 2000 system (Siemens Healthcare Diagnostics B.V., Breda, The Netherlands). Cortisol was measured with a chemiluminescent immunoassay (intra-assay
Serotonin transporters in obesity and insulin resistance

Insulin sensitivity

We used the homeostatic model assessment of insulin resistance (HOMA-IR) to assess insulin sensitivity. HOMA-IR is calculated from fasting plasma insulin and glucose and is shown to correlate with clamp derived peripheral glucose disposal rates (24).

\[
\text{HOMA-IR} = \frac{(\text{Fasting Plasma Glucose (mmol/L)} \times (\text{Fasting Plasma Insulin (mU/L)} \times 6.945))}{22.5}
\]

To determine whether subjects were insulin resistant or insulin sensitive, we used a cut-off value for insulin resistance >2.2 (25) and fasting insulin > 73.5 pmol/L (26). Insulin resistant obese subjects were stratified to the IRO group and insulin sensitive obese subjects to the ISO group.

Statistics

All data were analysed using SPSS for Windows, version 20.0 (SPSS Inc. Chicago, Illinois, USA). Data were tested for normality. To compare data between the lean and obese group, we used the Student’s T-test. We used 1-way ANOVA and a posthoc Bonferroni to evaluate data between the lean, ISO, and IRO groups. Within the obese group, ANCOVA was used with BMI as a covariate. Pearson correlation coefficients were calculated to investigate the relationship between SNS-BR and BMI as well as between SNS-BR and insulin sensitivity. For all analyses, a p < 0.05 was considered statistically significant and p < 0.1 was considered a trend. Sample size calculation was based on a previous study that showed that diencephalic SERT binding in lean subjects was 0.51±0.17 (20). To detect a difference with a significance level α=0.05, power=80%, variance of means = 0.029 and common standard deviation=0.17, we needed n=5 subjects per group (calculated with nQuery Advisor 7.0 software).
Results

Lean versus obese subjects
Baseline characteristics are presented in Table 1. As expected, the obese subjects had higher HOMA-IR, fasting plasma glucose, insulin and C-peptide concentrations compared to the lean controls. SERT binding in the diencephalon was not different between lean and obese subjects (0.89±0.32 vs 0.71±0.33, p=0.25) (Figure 2A). Since the hypothalamus plays a major role in regulation of glucose metabolism and food intake (27, 28) and reduced serotonergic signalling might contribute to body weight and insulin sensitivity, we studied SERT binding specifically within the hypothalamus. Hypothalamic SERT binding tended to be lower in obese subjects compared to lean subjects (1.12±0.73 vs 0.62±0.28, p=0.059) (Figure 2B). Striatal DAT binding did not differ between the lean and obese subjects (4.59±1.08 vs 4.99±1.18, p=0.46) (Figure 2C). BMI did not correlate with SERT and DAT binding within the obese or lean subjects (data not shown).

Insulin sensitive versus insulin resistant obese subjects
Since central serotonergic signalling might have independent effects on glucose metabolism or vice versa, we studied a body weight independent effect of insulin sensitivity on SERT and DAT and analysed subjects with low and high insulin sensitivity separately. We divided the obese group in an ISO and IRO group. BMI did not differ between ISO and IRO subjects while insulin, glucose and C-peptide concentrations were higher in the IRO subjects. HOMA IR was not significantly different between the insulin sensitive group and the lean controls. Fasting plasma glucagon and cortisol concentrations were not different between the three groups (Table 1). We found that the insulin resistant subjects had significantly lower diencephalic SERT binding compared to ISO (0.45±0.09 vs 0.97±0.27, p=0.009) and lean subjects (0.45±0.09 vs 0.89±0.32, p=0.019), while there was no difference between the lean and ISO subjects. ANCOVA revealed a significant effect on diencephalic SERT availability between ISO and IRO subjects, independent of BMI (adjusted mean 0.56±0.14 vs 1.08±0.15, p=0.009) (Figure 3A). Hypothalamic SERT binding did not differ between lean, IRO and ISO subjects (ANOVA, F=2.04, p=0.17) (Figure 3B). Moreover, no differences in striatal DAT binding were found between lean, ISO and IRO subjects (ANOVA, F=0.33, p=0.72) (Figure 3C). Insulin sensitivity and fasting insulin did not correlate with SERT or DAT binding within the obese (HOMA-IR r=-0.46, p=0.14 (SERT diencephalon), r=-0.16, p=0.64 (SERT hypothalamus) and r=0.03, p=0.92 (DAT); insulin r=-0.46, p=0.13 (SERT diencephalon), r=-0.17, p=0.62 (SERT hypothalamus) and r=-0.06, p=0.86 (DAT)) or lean (HOMA-IR r=0.53, p=0.18 (SERT diencephalon), r=0.70, p=0.08 (SERT hypothalamus) and r=-0.25, p=0.54 (DAT); insulin r=0.53, p=0.18 (SERT diencephalon), r=0.70, p=0.08 (SERT hypothalamus) and r=-0.25, p=0.56 (DAT)) subjects.
**Table 1. Baseline characteristics of study participants**

<table>
<thead>
<tr>
<th></th>
<th>Lean</th>
<th>Obese</th>
<th>ISO</th>
<th>IRO</th>
<th>ANOVA</th>
<th>Posthoc</th>
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<tr>
<td></td>
<td>p</td>
<td>F</td>
<td>ISO vs IRO</td>
<td>IRO vs lean</td>
<td>ISO vs lean</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>8</td>
<td>12</td>
<td>6</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>0.8</td>
<td>2:10</td>
<td>1.5</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>30.9 ± 10.5</td>
<td>31.3 ± 8.8</td>
<td>0.917</td>
<td>34.7 ± 9.9</td>
<td>28.0 ± 6.6</td>
<td>0.477</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.3 ± 1.3</td>
<td>36.6 ± 4.6</td>
<td>&lt;0.001</td>
<td>34.9 ± 3.8</td>
<td>38.3 ± 5.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>4.4 ± 0.4</td>
<td>4.9 ± 0.4</td>
<td>0.008</td>
<td>4.8 ± 0.3</td>
<td>5.0 ± 0.4</td>
<td>0.019</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>23 ± 13</td>
<td>106 ± 128</td>
<td>0.046</td>
<td>29 ± 11</td>
<td>184 ± 146</td>
<td>0.003</td>
</tr>
<tr>
<td>C-peptide (mg/mL)</td>
<td>499 ± 102</td>
<td>873 ± 402</td>
<td>0.009</td>
<td>655 ± 83</td>
<td>1092 ± 484</td>
<td>0.003</td>
</tr>
<tr>
<td>Cortisol (nmol/L)</td>
<td>468 ± 242</td>
<td>342 ± 157</td>
<td>0.172</td>
<td>271 ± 85</td>
<td>412 ± 188</td>
<td>0.185</td>
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<tr>
<td>Glucagon (ng/L)</td>
<td>73 ± 20</td>
<td>94± 31</td>
<td>0.114</td>
<td>95 ± 36</td>
<td>92 ± 28</td>
<td>0.291</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.7 ± 0.5</td>
<td>3.4 ± 4.2</td>
<td>0.045</td>
<td>0.9 ± 0.3</td>
<td>6.0 ± 4.8</td>
<td>0.003</td>
</tr>
</tbody>
</table>

ISO: insulin sensitive obese; IRO: insulin resistant obese. Data are presented as mean ± SD.
Figure 2. SERT and DAT binding in lean and obese subjects. 2A: diencephalic SERT binding; 2B: hypothalamic SERT binding and 2C: striatal DAT binding. Data are presented as mean ± SEM. # p=0.059.

Figure 3. SERT and DAT binding in lean versus insulin sensitive obese (ISO) and insulin resistant obese (IRO) subjects. 3A: diencephalic SERT binding; 3B: hypothalamic SERT binding (lean N=7, IRO N=5) and 3C: striatal DAT binding. Data are presented as mean ± SEM. * p<0.05 (one way ANOVA), ** p<0.01 (ANCOVA).
Discussion

We here show lower diencephalic SERT binding in insulin resistant subjects compared to lean and compared to equally obese, but insulin sensitive subjects. In addition, we found a trend towards lower SERT binding in the hypothalamus of obese subjects. Striatal DAT binding was not different between the lean and obese group nor between the IRO and ISO group.

To the best of our knowledge, this is the first study examining SERT binding in the human diencephalon in relation to insulin resistance in obesity. Previous imaging studies showed a negative correlation between BMI and diencephalic SERT binding in some (6) but not all (29-31) studies and data on insulin sensitivity were not reported.

Whether lower binding of SERT in our subjects is associated with reduced or increased synaptic serotonin is unknown. Acute inhibition of SERT function results in increased levels of extracellular serotonin (32), while chronic inhibition of SERT might result in decreased serotonergic signalling, given the detrimental long-term effects of SSRI use on food intake and body weight (33). In line, obese humans have lower serotonin metabolites in the cerebrospinal fluid compared to lean controls (8). Furthermore, SERT deficient mice have decreased expression of brain serotonin-2A/C receptors, while overexpression results in increased brain serotonin-2A/C receptors (34), suggesting that prolonged reduction of SERT corresponds with lower serotonergic signalling. Moreover, a decrease in synaptic serotonin levels has been reported to reduce SERT density and mRNA levels in rats (35), which may reflect a compensatory mechanism to maintain sufficient serotonin levels in the synaptic cleft. Also, acute reduction in synaptic serotonin levels induced lower SERT binding in a positron emission tomography (PET) study in baboons, which is contrary to what is predicted by a competition model (36). We therefore assume that a reduction in SERT binding reflects lower synaptic serotonin levels. Lower extracellular serotonin levels result in less inhibition of food intake and body weight gain (37) and could be either a cause or a consequence of obesity. Since diencephalic SERT binding was not different between insulin sensitive obese and lean subjects while SERT binding within the hypothalamus tended to be lower in all obese participants compared to the lean controls, lower extracellular serotonin specifically within the hypothalamus might contribute to the increased body weight in the obese group. Additionally, diet composition and pattern may have an independent effect on SERT binding, as we recently showed that in lean individuals a hypercaloric high-fat-high-sugar snacking diet reduces SERT binding in the diencephalon as assessed with $^{123}$I-FP-CIT SPECT (38). This is in line with previous data showing reduced serotonin concentrations in the hypothalamus after fat intake (39). We did not assess dietary intake and therefore cannot rule out a diet independent effect on SERT.

The underlying pathways explaining the relationship between insulin resistance and diencephalic SERT binding in humans remain speculative. We cannot distinguish between effects of insulin and/or glucose or other metabolic factors associated with insulin resistance, such as inflammatory proteins or adipokines,
on SERT binding. Furthermore, reduced SERT and/or serotonin might directly affect insulin sensitivity. Studies in humans indicate an increased risk of diabetes in subjects on SSRIs (40), although this does not necessarily implicate a central mechanism, and modulation of serotonergic signalling by targeting the serotonin-2C receptor or SERT itself affects glucose metabolism (4, 5). Furthermore SERT deficient mice develop obesity and exhibit glucose intolerance and insulin resistance (10). Moreover, manipulating central serotonergic activity affects glucose and insulin levels in rats, although the results are contradictory as peripheral infusion of glucose and insulin leads to a decrease (41) or increase in extracellular serotonin release respectively (42).

Based on the available data, we hypothesize that lower SERT in the diencephalon reduces serotonin signalling, which negatively affects glucose metabolism. Studies on in vivo differences in hypothalamic SERT in obese humans are lacking and although the available imaging techniques at present study do not allow for studying specific hypothalamic nuclei as a result of limited resolution, our findings are in line with an earlier report in which we showed lower SERT immunostaining in the hypothalamic infundibular nucleus of overweight and obese subjects (7). Lower serotonin signaling in the hypothalamus therefore might contribute to weight gain in humans. In contrast to the whole diencephalon, there was no difference in hypothalamic SERT binding between the insulin resistant and insulin sensitive group. This might indicate that the observed difference in diencephalic SERT binding between ISO and IRO is specific to a diencephalic region other than the hypothalamus. Scarce data show some potential areas of interest within the diencephalon besides the hypothalamus that might be related to peripheral glucose metabolism, including the thalamus and the epithalamus. However the role of serotonin, in relation to glucose metabolism, is not known in these areas. Non-obese type 2 diabetic Goto Kakizaki rats show decreased mRNA transcript levels of the pineal insulin receptors (43) and have lower serotonin and tryptophan levels in the pineal gland, which is part of the epithalamus (44). Furthermore, a lower increase in glucose levels within the thalamus was found in response to plasma hyperglycemia in type 1 diabetic humans compared to non-diabetic humans (45) suggesting a role for circulating insulin, although frontal and temporal cerebral metabolites, measured using spectroscopy, were not different under hyperinsulinemic conditions in the thalamus between lean men with high versus low insulin sensitivity (46). The currently used imaging tool does not have the spatial resolution to evaluate SERT binding in such small brain areas and translational research in rodents is needed to study this more in detail.

In contrast to the findings on SERT, we did not find a difference in striatal DAT binding between lean and obese subjects or IRO and ISO subjects. Although a recent rodent study reported that both striatal DAT and D2R density are decreased in diet-induced obesity (47), our data are consistent with two recently published European multi-centre 123I-FP-CIT SPECT studies in humans reporting no association between BMI and striatal DAT binding in lean and overweight humans (48, 49). Whereas DAT binding may not be affected by BMI in humans, we and others have previously reported on lower striatal dopamine D2/3R availability...
in obese compared to lean individuals (13), which suggests that lower D2/3R binding in obesity is not compensated by an increase of synaptic dopamine levels through a downregulation of DAT. Genetic factors might play an additional role in reduced striatal dopaminergic tone since adults with a polymorphism in the D2R gene, associated with compromised striatal dopamine signalling, are at high risk of becoming obese (50).

Our study has some limitations. First, the majority of our subjects were premenopausal women and our results remain to be validated in different age groups. Second, we studied men and women, while gender differences have been observed for striatal DAT (51) and diencephalic SERT binding (52), but not for hypothalamic SERT binding (31). However analyses of our results on SERT and DAT did not change after excluding the male subjects. Third, we used a mathematical model to calculate insulin sensitivity and although HOMA-IR correlates well with clamp-derived insulin sensitivity and therefore provides a good, commonly used and less invasive alternative to hyperinsulinemic euglycemic clamps (24), we cannot distinguish between liver and muscle insulin resistance in relation to SERT. Finally, although we used a brain-dedicated SPECT system, the presently used radiotracer $^{123}$FP-CIT is not selective as it binds in vivo to both SERT and DAT. Consequently, our results are in need of replication using a selective SERT tracer and PET.

In conclusion, SERT binding is reduced in the diencephalon of insulin resistant versus equally obese insulin sensitive subjects, showing a weight independent effect on SERT binding. Within the hypothalamus, SERT binding tends to be reduced in obese compared to lean humans independent of insulin sensitivity. It remains to be studied which structure within the diencephalon shows lower SERT in the insulin resistant state and whether interventions that increase SERT reduce insulin resistance or vice versa.
References


