CHAPTER 4

Cerebral blood flow and glucose metabolism in appetite-related brain regions in type 1 diabetic patients after treatment with insulin detemir and NPH insulin: a randomized-controlled cross-over trial

*Diabetes Care, in revision*

Larissa W. van Golen
Richard G. IJzerman
Marc C. Huisman
Jolanda F. Hensbergen
Roel P. Hoogma
Madeleine L. Drent
Adriaan A. Lammertsma
Michaela Diamant
CHAPTER 4. Insulin detemir versus NPH insulin effects measured with PET

ABSTRACT

Objective To test the hypothesis that insulin detemir, which is associated with less weight gain than other basal insulin formulations, exerts its weight modulating effects by acting on brain regions involved in appetite regulation, as represented by altered cerebral blood flow (CBF) and/or cerebral glucose metabolism (CMR$_{glu}$).

Research Design and Methods Twenty-eight male type 1 diabetic patients (age 36.9 ± 9.7 years, BMI 24.9 ± 2.7 kg/m$^2$, A1C 7.5 ± 0.6%) successfully completed a randomized cross-over study, consisting of 2 periods of 12 weeks treatment with either insulin detemir or NPH insulin, both in combination with prandial insulin aspart. After each treatment period, patients underwent positron emission tomography (PET) scans to measure regional CBF and CMR$_{glu}$.

Results After 12 weeks, A1C, daily insulin doses, fasting insulin and blood glucose levels were similar between treatments. Insulin detemir resulted in body weight loss, whereas NPH insulin induced weight gain (between-treatment difference 1.3 kg; $P = 0.02$). After treatment with insulin detemir relative to NPH insulin, CBF was higher in brain regions involved in appetite regulation, whereas no difference in CMR$_{glu}$ was observed.

Conclusions Treatment with insulin detemir versus NPH insulin resulted in weight loss, paralleled by increased CBF in appetite related brain regions in the resting state, in men with well-controlled type 1 diabetes. These findings lend support to the hypothesis that a differential effect on the brain may contribute to the consistently observed weight sparing effect of insulin detemir.

ClinicalTrials.gov, NTC00626080
INTRODUCTION

Intensive insulin therapy in type 1 diabetes helps patients to attain normoglycemia and improve long-term diabetes outcome. These benefits, however, may be offset by increased risk of hypoglycemia and body weight gain. Insulin detemir is a basal insulin analog that has weight sparing effects compared with other basal insulin formulations in both type 1 and type 2 diabetes (1), but to date the exact mechanisms underlying these effects have not been elucidated.

In contrast to its anabolic effects in peripheral tissues, in the brain, insulin acts as a satiety signal. These central effects have been established mainly in rodent studies, in which insulin was administered intra-cerebroventriculally (2;3). Effects of insulin on the human brain have been studied by intranasal insulin administration, which results in direct brain insulin uptake without systemic effects (4). A single dose of intranasal insulin intensified post-meal satiety in women (5) and decreased food intake in men (6), whereas 8-week intranasal insulin administration was associated with weight loss in men only (7).

It has been hypothesized that, in comparison with other insulin formulations, insulin detemir enters the brain more easily due to the fatty acid attached to the insulin molecule (8). Furthermore, insulin detemir is suggested to have stronger effects on brain functions than other basal insulin therapies: insulin detemir infusion in mice and healthy humans resulted in enhanced cortical activity compared with human insulin (as measured with electroencephalography (EEG) and magneto-encephalography (MEG)) and decreased food intake (9-11). These results suggest the existence of tissue specific kinetics of insulin detemir in the brain.

In addition to methods such as EEG and MEG, both of which measure neuronal activity in cortical areas only, positron emission tomography (PET) can be used to quantify metabolic effects of insulin within the whole brain. Using [18F]-2-fluoro-2-deoxy-D-glucose ([18F]FDG) and PET, it has been shown that the brain is sensitive to insulin with respect to its action on glucose uptake and metabolism (12;13). Also, based on the observed blunting of the effect of insulin on cerebral glucose metabolism (CMR_{glu}) in obese men with peripheral insulin resistance compared with lean insulin sensitive men, the existence of central insulin resistance in humans was postulated (14). CMR_{glu} is known to be closely linked to cerebral blood flow (CBF). The gold standard to obtain regional CBF in humans is [15O]H2O PET. Regional CBF (measured using SPECT) and cerebral blood flow velocity (measured by transcranial Doppler) were found to have a negative association with BMI in humans (15;16). The effects of insulin on CBF have not been investigated in humans, but in rats topically applied insulin increased cortical blood flow (17).

The purpose of the present study was to assess whether insulin detemir, as compared with NPH insulin, alters CBF and/or CMR_{glu} in appetite related brain regions in type 1 diabetic patients, as a potential mechanism contributing to the reported differential effects on body weight.
RESEARCH DESIGN AND METHODS

Subjects
From January 2009 until May 2011 patients were included in this randomized controlled cross-over trial; the last follow-up visit was on 13 December 2011. Thirty-five patients with type 1 diabetes, aged 18 to 60 years and with a BMI of 18-35 kg/m² were included; they were recruited from the outpatient clinic of the VU University Medical Center (VUMC) and from neighbouring hospitals. After giving written informed consent, all participants had a screening visit consisting of a medical history, physical examination and fasting blood and urine analyses. Exclusion criteria were diabetes duration less than 1 year, A1C > 8.5%, proliferative retinopathy, a history of recurrent severe hypoglycemia (defined as an episode that requires external assistance for recovery), a medical history of hypo unawareness, cardiovascular; renal or liver disease or severe head trauma, furthermore, any neurological or psychiatric disorder; endocrine diseases not well-controlled for the last three months, inability to undergo MRI scanning, substance abuse, the use of anticoagulants, oral steroids or any centrally acting agent. Of all patients in analysis, one had microalbuminuria, four stable background retinopathy and one peripheral neuropathy (Toronto score (18) of 9/19 and a vibration perception (19) threshold of > 25V at 5/12 locations). Three patients were treated with antihypertensive medication (one used an angiotensin II receptor antagonist (ARB), one an angiotensin converting enzyme inhibitor (ACEI) and an ARB, and one was treated with an ACEI, ARB, a diuretic and a calcium antagonist). Three patients used cholesterol lowering medication and one used aspirin as well. Two patients had stable hypothyroidism treated with thyroxin, and one had stable ulcerative colitis treated with mesalamin. The study was approved by the Medical Ethics Review Committee of the VUMC and the Central Committee on Research involving Human Subjects. The study was conducted according to the Declaration of Helsinki.

Protocol
The study was conducted in a randomized cross-over design, and part of a larger trial (ClinicalTrials.gov, NTC00626080). Primary outcomes were CBF and CMR_{glu} after a 12 week treatment period and change in body weight after this 12 week treatment was a secondary outcome measurement. After a run-in period of at least four weeks, during which the current insulin therapy was optimized, patients were randomly assigned to start with either insulin detemir or NPH insulin in the evening, both in combination with insulin aspart at mealtimes. Randomisation (block design) was conducted by the Trial Pharmacy of the VUMC and the assigned treatments were concealed by envelopes; a research physician (LWvG) enrolled patients in the study and assigned them to the intervention. After assignment no blinding was applied since NPH insulin needs to be mixed and visually inspected before injection. Weekly 7-point self-measured blood glucose curves were made and all fasting blood glucose levels were reported.
Where appropriate, basal insulin dose was adjusted to maintain a fasting glucose level of <7 mmol/L. Regular telephone contact was available for advice on basal and prandial insulin adjustments. After 12 weeks of treatment, patients switched from basal insulin.

The day prior to the scan session patients refrained from eating, alcohol and coffee from 22:00 h. They were instructed not to forget their basal insulin injection and, if possible, not to use any insulin aspart after their dinnertime injection. Patients arrived at the hospital at 7:15 h in a fasting state and remained fasted during the entire imaging procedure. Upon arrival an intravenous catheter was placed in an antecubital vein for blood collection and tracer injection. Blood glucose levels were checked and corrected if necessary (when glucose was <4 mmol/L and falling, or when glucose was >15 mmol/L). After checking for collateral circulation and administration of local anesthesia using intradermal 1% lidocaine, a radial artery was cannulated by an experienced anesthesiologist. Both cannulas were kept patent by a 3 IE/mL 0.9% NaCl heparin solution.

Before and immediately after scanning, patients completed a questionnaire, scoring their hunger (‘how hungry are you right now?’), fullness (‘how full are you at this moment?’), appetite (‘how much do you feel like eating right now?’), prospective consumption (‘how much could you eat right now?’), desire to eat (‘how strong is your desire to eat right now?’) and thoughts of eating (‘how much do you think about food right now?’) on a 10-point Likert scale. Furthermore, patients scored their insulin treatment satisfaction using the DTSQ, Diabetes Treatment Satisfaction Questionnaire, which measures satisfaction with treatment regimen, perceived frequency of hyperglycemia and perceived frequency of hypoglycemia over the past few weeks (20).

**Data acquisition**

One week prior to the PET scan, an MRI scan was performed. 3-D structural MRI images were acquired on a 3.0 T GE Signa HDxt scanner (General Electric, Milwaukee, Wisconsin, USA), using a T1-weighted fast Spoiled Gradient echo sequence.

PET scans were acquired at an HRRT (Siemens/CTI, Knoxville, TN, USA) PET scanner. The scanning protocol consisted of a $[^{15}O]$H$_2$O scan to measure CBF and an $[^{18}F]$FDG scan to measure CMR$_{glu}$. For details on scan protocol see (21). During both scans, arterial concentrations were monitored continuously and in addition manual samples were taken for cross-calibration of the measured input function. Samples obtained during the $[^{18}F]$FDG scan (15, 35 and 55 min post-injection) were also used to measure arterial plasma glucose levels. All scans were performed between 9:30 and 12:00 h to minimize diurnal variations.

**Data analyses**

List mode emission data were histogrammed into multi-frame sinograms, which subsequently were normalized, and corrected for randoms, dead time, decay, scatter and attenuation. Fully corrected sinograms were reconstructed using the standard 3D OP-OSEM reconstruction algorithm (22), resulting in 207 image
CHAPTER 4. Insulin detemir versus NPH insulin effects measured with PET

planes with 256 x 256 voxels and a voxel size of 1.22 x 1.22 x 1.22 mm$^3$(21). The effective spatial resolution of the reconstructed images was ~3 mm. MRI and PET images were co-registered using the software package VINCI (23). PET images were rebinned and PET and MRI images were cropped into a 128 x 128 matrix (21). Regions of interest (ROIs) were delineated on the MRI scan using the template defined in PVElab (24). Subsequently, all ROIs were projected onto the dynamic PET images, generating time activity curves (TACs) for the following 16 left and right regions: orbitofrontal cortex, anterior and posterior cingulate cortex, thalamus, insula, caudate nucleus, putamen, medial inferior frontal cortex, superior temporal cortex, parietal cortex, medial inferior temporal cortex, superior frontal cortex, occipital cortex, sensorimotor cortex, cerebellum, hippocampus, a single white matter region, a total grey matter region and striatum (putamen and caudate nucleus combined). Of these ROIs, the first 7 were of specific interest as these are involved in appetite regulation and reward. Using standard non-linear regression (NLR), appropriately weighted $[^{15}O]H_2O$ TACs were fitted to the standard one tissue compartment model (25) to obtain regional CBF values. In addition, parametric (voxel-wise) CBF images were generated from 6 mm full with at half maximum (FWHM) Gaussian smoothed dynamic $[^{15}O]H_2O$ images using a basis function method (BFM) implementation of the same model (26).

Using a standard NLR algorithm, appropriately weighted $[^{18}F]FDG$ TACs were fitted to an irreversible two tissue compartment model with 3 rate constants and blood volume as fit parameters. Next, the net rate of influx $K_i$ was calculated as $K_i k_f / (k_2 + k_3)$ with $K_i$ being the rate of transport from blood to brain, $k_2$ the rate of transport from brain to blood, and $k_3$ the rate of phosphorylation by hexokinase. Finally, $K_i$ was multiplied with the plasma glucose concentration and divided by a lumped constant (LC) of 0.81 (27) to obtain regional CMR$_{glu}$ values. In addition, parametric CMR$_{glu}$ images were generated using Patlak linearization (28).

Biochemical analyses
Capillary blood glucose (patient monitoring) was measured using a blood glucose meter (OneTouch ultra easy, LifeScan, Inc. Milpitas, CA, USA). Arterial glucose samples (to determine CMR$_{glu}$) were measured using the hexokinase method (Glucoquant; Roche Diagnostics, Mannheim, Germany). A1C was measured by cation-exchange chromatography (reference values: 4.3–6.1%; Menarini Diagnostics, Florence, Italy). Serum insulin concentrations were quantified using immunometric assays (Centaur; Siemens Diagnostics, Deerfield, IL); insulin detemir levels were divided by four to compensate for the difference in molar dose ratio relative to NPH insulin. Urine microalbumin was quantified using immunonefelometry (Immage 800, Beckman Coulter, Brea, CA).

Statistical analysis
Data are expressed as mean ± SD. Skewed data and ordinal values are expressed as median and inter-quartile (IQ) range. Differences between both insulin treatments were tested by repeated measures analysis or Wilcoxon signed-rank
test (insulin detemir versus NPH insulin). Analyses were performed using SPSS for Windows, version 20.0 (SPSS, Chicago, IL). $P < 0.05$ was considered to be statistically significant.

Parametric images were analysed using SPM8 software (Wellcome Trust Centre for Neuroimaging, UK). Parametric images were smoothed using a 6 mm FWHM Gaussian kernel, co-registered to corresponding T1-weighted MRI images and normalized to MNI space. Paired t-tests were performed (insulin detemir versus NPH insulin).

Using data of 18 paired H$_2$O PET measurements and an expected difference in total grey matter CBF of 15% (0.046 ± 0.05 mL·cm$^{-3}$·min$^{-1}$), our study had a power of 96% (alpha 0.05) to detect differences between treatment with insulin detemir and NPH insulin. Using 24 paired FDG PET data and an expected difference in total grey matter CMR$_{glu}$ of 7.5% (0.011 ± 0.02 μmol·cm$^{-3}$·min$^{-1}$), our study had a power of 73% to detect differences between treatments.

**RESULTS**

During the study, one patient dropped out in his first treatment period (due to NPH insulin schedule difficulties) and one in the second period (due to a hip fracture). Due to technical problems ($n = 2$) and patient movement ($n = 2$), combined [$^{18}$F]FDG and [$^{15}$O]H$_2$O data were discarded for these four subjects. [$^{15}$O]H$_2$O was not available for one patient on both occasions and for three patients on one occasion. After quality control of the remaining scans, paired CMR$_{glu}$ data were available in 24 patients and paired CBF measurements in 18 patients. Subject characteristics of all 28 patients included in the analyses are listed in Table 4.1. At the end of the treatment period, daily insulin doses and A1C did not differ between treatment (Table 4.2). Insulin detemir decreased body weight by 0.7 kg, whereas NPH insulin increased weight by 0.6 kg (between-treatment difference 1.3 kg, $P = 0.02$; Table 4.2). Perceived hyperglycemia and hypoglycemia did not differ significantly between treatments (DTSQ); patient satisfaction was significantly greater when using insulin detemir than NPH insulin ($P = 0.003$).

Irrespective of the treatment arm, patients scored 5 out of 6 items (hunger, appetite, prospective consumption, desire to eat and thoughts of eating) significantly higher after the scan than before the scan ($P < 0.01$ for each item), indicating that appetite increased during the scanning period (all were fasting). When treated with insulin detemir, patients scored higher on the 6th item, i.e., fullness, after the PET scan than patients treated with NPH insulin (mean (IQ range): 4.0 (3.0-5.0) versus 3.0 (2.0-4.0), $P = 0.03$ for between-group difference).

On the day of the PET scan, three patients treated with insulin detemir had to consume some carbohydrates to prevent or resolve a mild hypoglycemia several hours before PET scanning and six patients received ~20 mL 20% glucose intravenously (iv) before the scan to prevent hypoglycaemia. Three patients that were treated with NPH insulin consumed some carbohydrates at getting up because of low or falling blood glucose level and two patients received ~15
CHAPTER 4. Insulin detemir versus NPH insulin effects measured with PET

mL 20% glucose iv well before the PET scan started. In all patients average arterial glucose level was stable within 10% and above 5.0 mmol/L during data acquisition.

NLR analysis showed that CBF was higher in all regions after treatment with insulin detemir. Of interest, this was significant in most appetite related brain regions: bilateral insula, bilateral putamen and right caudate nucleus, right thalamus, bilateral anterior and right posterior cingulate cortices, when patients received insulin detemir versus NPH insulin (Table 4.3). In addition, higher CBF was observed in right medial inferior frontal cortex, bilateral parietal cortex and bilateral sensorimotor cortex (all $P < 0.05$) after treatment with insulin detemir versus NPH insulin. Results were similar after exclusion of patients using antihypertensive medication ($n = 3$) and after exclusion of the one left-handed patient. After adjustment for A1C, glucose and insulin levels, CBF differences in appetite related regions remained unaltered (data not shown). No significant correlation between changes in CBF and changes in glucose, insulin and A1C levels or body weight were found. Regional analyses of parametric images showed good correlation with regional NLR analyses (slope = 0.99, $R^2 = 0.93$, for $N = 5$ NPH and $N = 5$ insulin detemir; data not shown; similar to data obtained in healthy subjects (21)). These parametric analyses (voxel-level) did not provide additional findings relative to regional NLR analyses.

Table 4.1 Patient characteristics

<table>
<thead>
<tr>
<th>N</th>
<th>28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36.9 ± 9.7</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>12.8 (6.0-17.0)</td>
</tr>
<tr>
<td>Pre-trial insulin detemir, n (%)</td>
<td>9 (32%)</td>
</tr>
<tr>
<td>Pre-trial NPH insulin, n (%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Pre-trial insulin glargine, n (%)</td>
<td>18 (64%)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>82.4 ± 12.7</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>24.9 ± 2.7</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>117 ± 9</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>78 ± 7</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>7.5 ± 0.6</td>
</tr>
<tr>
<td>Total Cholesterol (mmol/L)</td>
<td>4.5 ± 0.6</td>
</tr>
<tr>
<td>HDL Cholesterol (mmol/L)</td>
<td>1.4 ± 0.4</td>
</tr>
<tr>
<td>LDL Cholesterol (mmol/L)</td>
<td>2.5 ± 0.6</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.1 ± 0.5</td>
</tr>
<tr>
<td>Urine albumin: creatinine ratio (mmol/mg)</td>
<td>1.1 ± 2.9</td>
</tr>
</tbody>
</table>

Data are mean ± SD or median (IQ range), absolute numbers or proportions (in %).
Table 4.2 Clinical characteristics before and at the end of each treatment period

<table>
<thead>
<tr>
<th>Patient characteristics (n = 28)</th>
<th>NPH insulin</th>
<th>Insulin detemir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg), t = 0 weeks</td>
<td>82.7 ± 12.6</td>
<td>83.1 ± 12.6</td>
</tr>
<tr>
<td>Body weight (kg), t = 12 weeks</td>
<td>83.4 ± 13.0</td>
<td>82.4 ± 12.4*</td>
</tr>
<tr>
<td>Delta body weight (kg)</td>
<td>0.6 ± 1.9</td>
<td>-0.7 ± 1.8*</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>112 ± 10</td>
<td>113 ± 9</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>75 ± 7</td>
<td>76 ± 5</td>
</tr>
<tr>
<td>A1C (%), t = 0 weeks</td>
<td>7.3 ± 0.6</td>
<td>7.4 ± 0.6</td>
</tr>
<tr>
<td>A1C (%), t = 12 weeks</td>
<td>7.4 ± 0.6</td>
<td>7.4 ± 0.6</td>
</tr>
<tr>
<td>Daily insulin dose, 12w (basal) (IU/day)</td>
<td>25.9 ± 11.0</td>
<td>26.5 ± 10.1</td>
</tr>
<tr>
<td>Daily insulin dose, 12w (aspart) (IU/day)</td>
<td>31.4 ± 11.8</td>
<td>31.0 ± 11.2</td>
</tr>
<tr>
<td>Serum insulin (pmol/L) during PET</td>
<td>75.6 (62.0-110.7)</td>
<td>85.6 (58.4-119.3)</td>
</tr>
<tr>
<td>Blood glucose (mmol/L) during PET</td>
<td>10.7 ± 2.9</td>
<td>9.9 ± 3.1</td>
</tr>
</tbody>
</table>

Data are mean ± SD or median (IQ range); * P < 0.05 for treatment effect; t, time.

During the [18F]FDG scan, mean arterial plasma glucose levels did not differ between treatments; serum insulin levels were similar as well (Table 4.2). NLR analysis showed no significant differences in CMR_{glu} in appetite related predefined (PVElab) regions (Table 4.3). No significant differences in transport parameters for total grey matter (K_i, K_e, k_1, k_2), were observed (data not shown) and total grey matter CMR_{glu} did not differ significantly between treatments (0.15 ± 0.02 μmol·cm^{-3}·min^{-1} after treatment with NPH insulin versus 0.16 ± 0.02 μmol·cm^{-3}·min^{-1} after treatment with insulin detemir). Parametric analyses yielded similar results (data not shown).

**DISCUSSION**

The main finding of this study was that a relative loss in body weight in type 1 diabetic patients treated with insulin detemir was accompanied by an increase in CBF in insula, thalamus, anterior and posterior cingulate cortex and striatum, regions that are involved in appetite regulation and reward. In contrast, no significant differences in cerebral glucose metabolism between groups were found.

Several studies have investigated the effects of body weight on CBF. Some of these studies suggest that changes in CBF are causal in the development of obesity. CBF responses in appetite related regions to a meal in formerly obese persons were similar to those in obese persons, but different from those in lean subjects (29), indicating a predisposition to obesity that may involve areas of the brain that control complex aspects of eating behaviour. This is in line with
Table 4.3 Regional PET-measured CMR$_{glu}$ and CBF at the end of each intervention period

<table>
<thead>
<tr>
<th>Region of interest</th>
<th>CMR$_{glu}$</th>
<th>CBF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NPH detemir</td>
<td>P</td>
</tr>
<tr>
<td>Total GM</td>
<td>0.15 ± 0.02</td>
<td>0.16 ± 0.02</td>
</tr>
<tr>
<td>Regions of interest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OFC L</td>
<td>0.18 ± 0.03</td>
<td>0.18 ± 0.02</td>
</tr>
<tr>
<td>OFC R</td>
<td>0.18 ± 0.03</td>
<td>0.18 ± 0.02</td>
</tr>
<tr>
<td>Insula L</td>
<td>0.17 ± 0.03</td>
<td>0.17 ± 0.03</td>
</tr>
<tr>
<td>Insula R</td>
<td>0.17 ± 0.03</td>
<td>0.17 ± 0.03</td>
</tr>
<tr>
<td>Putamen L</td>
<td>0.21 ± 0.04</td>
<td>0.22 ± 0.03</td>
</tr>
<tr>
<td>Putamen R</td>
<td>0.21 ± 0.04</td>
<td>0.22 ± 0.03</td>
</tr>
<tr>
<td>Caudate L</td>
<td>0.19 ± 0.05</td>
<td>0.20 ± 0.04</td>
</tr>
<tr>
<td>Caudate R</td>
<td>0.19 ± 0.04</td>
<td>0.20 ± 0.03</td>
</tr>
<tr>
<td>Striatum</td>
<td>0.21 ± 0.04</td>
<td>0.22 ± 0.03</td>
</tr>
<tr>
<td>Thalamus L</td>
<td>0.18 ± 0.03</td>
<td>0.19 ± 0.03</td>
</tr>
<tr>
<td>Thalamus R</td>
<td>0.18 ± 0.03</td>
<td>0.19 ± 0.03</td>
</tr>
<tr>
<td>Cingulate ant L</td>
<td>0.16 ± 0.03</td>
<td>0.17 ± 0.03</td>
</tr>
<tr>
<td>Cingulate ant R</td>
<td>0.16 ± 0.02</td>
<td>0.17 ± 0.03</td>
</tr>
<tr>
<td>Cingulate post L</td>
<td>0.21 ± 0.03</td>
<td>0.22 ± 0.04</td>
</tr>
<tr>
<td>Cingulate post R</td>
<td>0.22 ± 0.03</td>
<td>0.22 ± 0.04</td>
</tr>
</tbody>
</table>

Mean ± SD. Paired data, n = 24 for CMR$_{glu}$ and n = 18 for CBF. CMR$_{glu}$, cerebral glucose metabolism, in μmol ·cm$^{-3}$·min$^{-1}$; CBF, cerebral blood flow, in mL·cm$^{-3}$·min$^{-1}$; GM, grey matter; L, left; R, right; OFC, orbitofrontal cortex; ant, anterior; post, posterior.

The observed increase in CBF in appetite regulating brain regions in response to meal consumption in successful dieters (30). In minipigs, however, diet induced obesity resulted in a decrease in CBF in several of these brain regions, suggesting that the changes in CBF were the result of weight gain (31). From the present study, it is not possible to determine whether increases in CBF in patients treated with insulin detemir are cause or consequence of the observed weight loss. Previous studies in mice and healthy humans, however, showed cortical brain activation upon acute insulin detemir versus human insulin infusion with concomitant decrease in food intake (9-11). In addition, it was shown that insulin-induced glucose lowering in type 1 diabetic patients resulted in an increase in CBF (32;33). However, whether this was caused by increasing insulin
or by decreasing glucose levels could not be determined in those studies. Still, a
direct effect of insulin on the brain is supported by the acute effects of insulin on
cerebrovascular responses in rats (17).
In contrast to the differential effects on CBF, the two insulin treatments did
not result in significant differences in CMR_{glu} in any of the regions investigated.
Previous studies have shown an inverse association of CMR_{glu} and BMI (34), and
increases in CMR_{glu} after stimulation with food pictures (35;36). Of note, the
increase in CMR_{glu} in appetite related brain regions following insulin infusion
was blunted in insulin resistant men compared with insulin sensitive men (14)
and it was associated with insulin resistance and overweight. Taken these and
the present findings together, it can be concluded that although insulin may have
an enhancing effect on glucose metabolism in appetite regulating brain regions,
no important additional role for insulin detemir is observed in the resting state.
Possible confounders that could have accounted for the differences in CBF include
A1C or prevailing glucose and insulin levels. However, these parameters were
not significantly different between treatments, and the insulin detemir induced
increase in CBF was similar after adjustment for A1C, glucose, and insulin levels.
Limitations of this study include its non-blinded nature due to differences in insulin
formulations. NPH insulin is a cloudy suspension that needs to be thoroughly
stirred before injection, whereas insulin detemir is a clear, colourless solution
that does not require stirring. Therefore, it was not possible to perform a double-
blind study. Worldwide, however, NPH insulin is the standard (intermediate)
long-acting human insulin and, therefore, the best active comparator. Moreover,
even if patients were aware of the type of insulin treatment, it is unlikely that this
will have had an effect on the present findings.
Although weight gain associated with insulin treatment is relevant for type 1
diabetes patients, it is especially important for patients with type 2 diabetes.
It is tempting to generalize the present findings to type 2 diabetes, but further
studies in these patients are needed, especially since central insulin resistance
possibly plays a role in type 2 diabetes.
The present study focused on insulin detemir action in the brain. It should be
noted, however, that other mechanisms have been proposed to explain its weight
reducing effect. These include less defensive eating due to less hypoglycemia,
increased energy expenditure, and higher insulin levels in the liver compared
with peripheral tissue, although none of these could be firmly established (37-
40). In the present study, no significant differences in perceived hypoglycemia
frequency were found between treatments.
In conclusion, the present findings support the hypothesis that a differential
effect on CBF, measured during a resting, fasting condition, may contribute to the
consistently observed weight sparing effect of insulin detemir treatment.
REFERENCE LIST

Insulin detemir versus NPH insulin effects measured with PET. CHAPTER 4


95
CHAPTER 4. Insulin detemir versus NPH insulin effects measured with PET

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