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Hypothalamic insulin responsiveness is associated with pancreatic insulin secretion in humans

Stephanie Kullmann[a,b,c], Andreas Fritsche[a,b,c,*], Robert Wagner[a,b,c], Sophia Schwab[a], Hans-Ulrich Häring[a,b,c,e], Hubert Preissl[a,b,c,d,e,f], Martin Heni[a,b,c]

[a] Department of Internal Medicine, Division of Endocrinology, Diabetology, Angiology, Nephrology and Clinical Chemistry, Eberhard Karls University Tübingen, Tübingen, Germany
[b] Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the University of Tübingen, Tübingen, Germany
[c] German Center for Diabetes Research (DZD e.V.), Tübingen, Germany
[d] Institute of Pharmaceutical Sciences, Department of Pharmacy and Biochemistry, Eberhard Karls University Tübingen, Tübingen, Germany
[e] Interfaculty Centre for Pharmacogenomics and Pharma Research at the Eberhard Karls University Tübingen, Tübingen, Germany
[f] Institute for Diabetes and Obesity, Helmholtz Diabetes Center, Helmholtz Center Munich, German Research Center for Environmental Health (GmbH), Neuherberg, Germany

ABSTRACT

Context: Activity of the hypothalamus – the major brain area controlling peripheral metabolism – is specifically modulated by insulin. Research in animals suggests that brain insulin action influences pancreatic insulin secretion.

Objective: We investigated the association between hypothalamic insulin sensitivity and pancreatic insulin secretion in humans.

Design and Setting: This was a clinical-experimental trial in an university hospital setting.

Participants: 48 healthy volunteers (21 women and 27 men) were included.

Main outcome measures: Insulin sensitivity of the hypothalamus was quantified by cerebral blood flow (CBF) using MRI in combination with intranasal insulin administration. On a different day, a 75 g oral glucose tolerance test with glucose, insulin, and C-peptide levels measured at five time points was performed. Three established insulin secretion indices (insulinogenic index [IGI], corrected insulin response [CIR], and $AUC_{C\text{-}peptide0\text{–}30}/AUC_{glucose0\text{–}30}$) were then analyzed for correlations with hypothalamic insulin sensitivity independent of whole-body insulin sensitivity.

Results: Hypothalamic insulin sensitivity showed a significant association with all three investigated insulin secretion indices (IGI $p = 0.0043$; CIR $p = 0.06$; $AUC_{Cpep0\text{–}30}/AUC_{gluc0\text{–}30}$ $p = 0.0179$). Participants with a strong hypothalamic insulin effect (i.e. decreased CBF after intranasal insulin administration) had lower insulin secretion during the OGTT, whereas participants with hypothalamic insulin resistance had substantially higher insulin secretion. No correlations with the occipital cortex, a control region, were detected.

Conclusions: Our data suggest that hypothalamic insulin resistance might contribute to pancreatic insulin hypersecretion. Alternatively, common pathogenetic mechanisms could introduce both brain insulin resistance and beta cell hypersecretion.

1. Introduction

Glucose tolerance is determined by two main components: Insulin secretion and insulin sensitivity. When the balance between the two is disturbed, glucose tolerance deteriorates and type 2 diabetes subsequently develops.

Research over the last few years has provided evidence that peripheral insulin sensitivity is modulated by the brain [1]. In a number of studies in humans on this topic, insulin was delivered to the brain via intranasal application [2–5]. When insulin is administered as a nasal spray, the hormone rapidly reaches the brain and remains there for a considerable period of time [6]. During intranasal insulin application, only small amounts of the peptide are absorbed into the bloodstream from where they are rapidly cleared thereafter [2]. Thus, insulin nasal spray is a useful tool for studying the effects of the hormone on the human brain. Using this technique, we recently

* Corresponding author at: Universitatsklinikum Tübingen, Medizinische Klinik IV, Otfried-Muller-Str 10, 72076 Tübingen, Germany.
E-mail address: andreas.fritsche@med.uni-tuebingen.de (A. Fritsche).

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characterized the hypothalamus as a major insulin-sensitive brain area [7].

Insulin delivery to the human brain via the intranasal approach modulates the estimated insulin sensitivity at fasting [2], reduces the amount of peripheral insulin necessary to control glucose during a meal [8], suppresses endogenous glucose production [4], and increases glucose infusion rates during a hyperinsulinemic-euglycemic glucose clamp [3]. All these observations indicate improved whole-body insulin sensitivity due to brain insulin action. However, this mechanism is not uniformly present in all participants: intranasal insulin failed to improve peripheral insulin sensitivity in overweight and obese humans [3], who are known to be insulin-resistant in the brain [1].

In humans, we have practically no data on the role of the brain with regard to insulin secretion capacity – the second major component of glucose tolerance. However, research in animals points towards an important role of the brain [9–11].

Insulin is produced in pancreatic beta cells from where it is released in response to rising glucose levels. Their insulin-releasing properties are influenced not only by several circulating factors, but also by the neuronal innervation of pancreatic islets [10–12]. This is underscored by the observation that neuronal inputs can promote insulin secretion even in the absence of any change in blood glucose during the cephalic phase, i.e., during anticipation of food intake [13,14]. This conditioned reflex originates in the brain and probably reaches pancreatic beta cells via both branches of the autonomic nervous system [11,14,15].

Besides this brain-derived effect on insulin secretion in the fasting state, research in animals suggests that, when insulin is released physiologically, the brain exerts comparable effects in the postprandial state also. The best studied factor in this context is glucose, which regulates beta cell function via glucose sensitive neurons (reviewed e.g., in [10]). Of note, brain effects of insulin itself may also contribute to this postprandial mechanism. Injection of insulin into the brains of dogs stimulated pancreatic insulin release [16,17] independent of brain glucose concentrations [17]. This response was attenuated when experiments were performed in vagotomized animals [17], an observation pointing to the parasympathetic nervous system as one of the effectors. The autonomic nervous system also responds to brain insulin action in humans [3,18], albeit the effects on pancreatic beta cell function have not yet been addressed.

We therefore aimed to study the relationship between insulin action in the human hypothalamus and pancreatic insulin secretion. We hypothesize that hypothalamic brain insulin sensitivity correlates with beta cell response after an oral glucose load.

2. Methods

2.1. Participants

48 volunteers (21 women and 27 men) from our recent [7] and an ongoing project with complete fMRI and OGTT data sets were included in this analysis. Their mean age was 26.7 years (range 21–40) while their mean BMI was 26.9 kg/m^2 (range 19.2–46.5). Detailed clinical characteristics are presented in Table 1. The participants had no relevant chronic conditions and were certified as healthy by a physician (except for obesity in part of the studied group). Participants were not taking any medication (except oral contraceptives). Informed written consent was obtained from all participants, and the local Ethics Committee approved the protocol.

2.2. Oral glucose tolerance test (OGTT)

Following an overnight fast, participants ingested a 75 g OGTT solution between 08:00 h and 09:00 h (Accu-Check Dextrose OGT, Roche Diagnostics, Germany). Venous blood samples were taken at 0, 30, 60, 90, and 120 min post glucose ingestion. A bedside glucose analyzer (glucose-oxidase method, YSI - Yellow Springs Instruments, Yellow Springs, CO, USA) was used to determine plasma glucose from these samples and plasma insulin and C-peptide concentrations were measured by commercial chemiluminescence assays for ADVIA Centaur (Siemens Medical Solutions, Fernwald, Germany).

Table 1
Clinical characteristics of the study participants.

	Mean	Range
N (f/m)	48 (21/27)	
Age (years)	26.7	21–40
BMI (kg/m^2)	26.9	19.2–46.5
Fasting glucose (mmol/l)	5.1	4.1–6.7
Glucose, 2 h OGTT (mmol/l)	5.9	3.4–10.1
Fasting insulin (pmol/l)	77	25–236
OGTT-derived insulin sensitivity index (AU)	12.7	0.9–32.9
HbA1c (%)	5.2	4.4–5.9
HbA1c (mmol/mol)	33.6	24–41

BMI – body mass index; HbA1c – glycosylated hemoglobin; OGTT – oral glucose tolerance test.

2.3. Calculations

Peripheral insulin sensitivity was estimated according to Matsuda and DeFronzo [19] as $10{,}000/(G_0 \times I_0 \times G_{mean} \times I_{mean})^{1/2}$ with G = glucose and I = insulin.

Insulin secretion during the OGTT was estimated [20] as:

Insulinogenic index (IGI), calculated as: $(I_{30} - I_0)/(G_{30} - G_0)$.

Corrected insulin response (CIR), calculated as: $100 \times I_{30}/[G_{30} \times (G_{30} - 3.89)]$.

Areas under the curve (AUC) were calculated according to the trapezoid method.

2.4. Functional magnetic resonance imaging (fMRI)

On a different day, all participants underwent fMRI to assess regional insulin sensitivity of the brain. Experiments were conducted after an overnight fast of at least 10 h and commenced at 7.00 a.m. with a pulsed arterial spin labeling (PASL) measurement under basal condition to quantify cerebral blood flow (CBF). Following the basal measurement, 160 units of human insulin were administered as nasal spray as previously described [3]. After 30 min, PASL was assessed a second time.

2.5. fMRI data acquisition

Whole-brain fMRI data was obtained with a 3.0 T scanner (Siemens Tim Trio, Erlangen, Germany). As previously described [7], PASL images were obtained with a PICORE-Q2TIPS (proximal inversion with control for off-resonance effects – quantitative imaging of perfusion using a single subtraction) sequence. Each measurement consisted of 79 alternating tag and control images with the following imaging parameters: inversion time (TI), TI1 = 700 ms, TI2 = 1800 ms, repetition time (TR) = 3000 ms, echo time (TE) = 19 ms, inplane resolution = 3 × 3 mm^2, field of view = 192 mm, matrix size 64 × 64 and flip angle = 90°. In addition, a high-resolution T1-weighted anatomical image was acquired.

2.6. Image processing

As previously reported [7], image preprocessing was performed using the ASLtbx with SPM8 (Wellcome Trust Centre for Neuroimaging). The general kinetic model was used for absolute perfusion quantification. Perfusion images were generated by calculating the control-tag differences by surround subtraction. For accurate CBF quantification (ml × 100 g^{-1} x min^{-1}), we used an M0 map instead