Effects of Insulin on Brain Glucose Metabolism in Impaired Glucose Tolerance

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OBJECTIVE—Insulin stimulates brain glucose metabolism, but this effect of insulin is already maximal at fasting concentrations in healthy subjects. It is not known whether insulin is able to stimulate glucose metabolism above fasting concentrations in patients with impaired glucose tolerance.

RESEARCH DESIGN AND METHODS—We studied the effects of insulin on brain glucose metabolism and cerebral blood flow in 13 patients with impaired glucose tolerance and nine healthy subjects using positron emission tomography (PET). All subjects underwent PET with both [^{18}F]fluorodeoxyglucose (for brain glucose metabolism) and [^{15}O]H_2O (for cerebral blood flow) in two separate conditions (in the fasting state and during a euglycemic-hyperinsulinemic clamp). Arterial blood samples were acquired during the PET scans to allow fully quantitative modeling.

RESULTS—The hyperinsulinemic clamp increased brain glucose metabolism only in patients with impaired glucose tolerance (whole brain: +18%, $P = 0.001$) but not in healthy subjects (whole brain: +3.9%, $P = 0.373$). The hyperinsulinemic clamp did not alter cerebral blood flow in either group.

CONCLUSIONS—We found that insulin stimulates brain glucose metabolism at physiological postprandial levels in patients with impaired glucose tolerance but not in healthy subjects. These results suggest that insulin stimulation of brain glucose metabolism is maximal at fasting concentrations in healthy subjects but not in patients with impaired glucose tolerance.
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Peripheral insulin resistance is a hallmark of metabolic syndrome and type 2 diabetes, but it is unclear if the brain also shows insulin resistance. Peripheral insulin crosses the blood-brain barrier via an active transport mechanism and binds to insulin receptors on neurons and glial cells. Insulin has a catabolic effect; in addition, it influences memory functions by modulating neurotransmitter release and synaptic plasticity (1–4). Therefore, determining whether insulin resistance also occurs in the brain in metabolic syndrome is important (5). Obese individuals have a decreased cerebrospinal fluid–to–plasma insulin ratio (6), diminished catabolic responses to intranasal insulin (7), and decreased cortical brain activity after insulin (8), suggesting brain insulin resistance (1,5). However, these indirect studies do not establish the relationship between insulin and brain glucose metabolism, which is important given the role of the brain in glucose sensing (9).

Direct evidence on the effects of insulin on the brain may be obtained with positron emission tomography (PET) and ^{18}F-labeled fluorodeoxyglucose ([^{18}F]FDG). Studies in healthy subjects have shown that brain glucose metabolism does not increase after increasing plasma insulin concentrations above physiological fasting levels (10,11) but decreases after decreasing plasma insulin concentration below physiological fasting levels (12,13), suggesting that the insulin effect is already saturated at fasting concentrations in healthy subjects. In contrast, Anthony et al. (12) recently demonstrated that reducing plasma insulin does not reduce brain glucose metabolism in patients with impaired glucose tolerance. However, it is not known whether insulin stimulates brain glucose metabolism above fasting levels in these patients or whether this effect is already saturated at fasting levels, as in healthy subjects (12,13).

To characterize the dose-response relationship of plasma insulin and brain glucose metabolism in patients with impaired glucose tolerance, we used [^{18}F]FDG PET to measure brain glucose metabolism in two conditions (in the fasting state and during a euglycemic-hyperinsulinemic clamp) in both healthy subjects and patients with impaired glucose tolerance. [^{18}F]FDG is a glucose analog that is taken up in the brain and trapped after phosphorylation; thus, the measured signal approximates uptake of glucose. The euglycemic-hyperinsulinemic clamp allows close monitoring and adjustment of plasma glucose while inducing a constant insulin stimulation. In a subset of subjects, we also measured the effects of insulin on cerebral blood flow with [^{15}O]H_2O PET.

RESEARCH DESIGN AND METHODS

Twenty-two subjects (Table 1), classified either as healthy or as having impaired glucose tolerance (14), were recruited to participate in two PET studies performed during the fasting state and euglycemic-hyperinsulinemia in separate days in randomized order. The PET studies measured brain glucose metabolism with [^{18}F]FDG (13 patients, nine healthy) and blood flow with [^{15}O]H_2O (six patients, eight healthy). All subjects were not studied with [^{15}O]H_2O because this scan was omitted from the study based on interim results. All subjects gave their written informed consent after the study had been approved by the ethics committee of the hospital district of southwestern Finland.

Euglycemic-hyperinsulinemic clamp. The euglycemic-hyperinsulinemic clamp ($1\ mU \cdot kg^{-1} \cdot min^{-1}$) technique was used during the PET scan, as previously described (15,16).

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TABLE 1
Demographic and metabolic characteristics of the study groups

Characteristics	Healthy subjects	Impaired glucose tolerance	*P*
n	9	13	
Baseline data			
Sex (female/male)	4/5	8/5	0.6
Age (years)	38 ± 12	49 ± 8	0.04
Weight (kg)	75 ± 10	112 ± 20	<0.001
BMI (kg/m^2)	24 ± 2	38 ± 8	<0.001
Fat (bioimpedance) (%)	28 ± 4	44 ± 9	<0.001
Waist circumference (cm)	85 ± 10	119 ± 14	<0.001
Fasting plasma glucose (mmol/L)	5.3 ± 0.5	5.9 ± 0.5	0.01
2-h oral glucose tolerance test (plasma glucose) (mmol/L)	5.1 ± 1.0	8.6 ± 1.0	<0.001
During PET: fasting state			
Plasma glucose (mmol/L)	5.4 ± 0.4	5.8 ± 0.6	0.06
Serum insulin (mU/L)	4 ± 3	11 ± 4	<0.001
During PET: hyperinsulinemia			
Plasma glucose (mmol/L)	5.1 ± 0.3	4.8 ± 0.8	0.2
Serum insulin (steady state) (mU/L)	58 ± 5	73 ± 19	0.02
Whole-body glucose uptake (*M* value) (μmol · kg^{-1} · min^{-1})	30.3 ± 6.0	11.9 ± 4.2	<0.001

Data are means ± SD.

PET acquisition. The PET studies were performed after a 12-h fast using the General Electric Advance PET camera (General Electric Medical Systems, Milwaukee, WI) (16). The [^{15}O]H_2O PET scan started at 45 min and the [^{18}F]FDG scan at 60 min after the position to the scanner or the start of euglycemic-hyperinsulinemic clamp. The synthesis (17,18) and image acquisition (16,19) of [^{15}O]H_2O and [^{18}F]FDG were performed as previously described.

Quantification of brain glucose metabolism. Glucose metabolism (CMRglu; μmol · 100 g^{-1} · min^{-1}) was calculated for each voxel separately using the linear Gjedde-Patlak plot with the arterial plasma input function (linear start time 10 min) as previously described (20). CMRglu images were normalized into standard space as previously described (21) using SPM5 (www.fil.ion.ucl.ac.uk/spm/) running on Matlab for Windows (version 7.3.0.267; Math Works, Natick, MA). Regions of interest (frontal cortex, temporal cortex, parietal cortex, occipital cortex, mesial temporal cortex, insula, striatum, cerebellum, and thalamus) were applied in standard space using Imadeus software (version 1.2.; Forima, Turku, Finland) to obtain glucose metabolism values. Hypothalamus was not included because it is too small to be reliably quantified.

Quantification of cerebral blood flow. Cerebral blood flow (mL · 100 g^{-1} · min^{-1}) was calculated for each voxel separately based on a one-tissue compartmental model using the arterial radioactivity concentration as the input function as previously described (19). Image analysis for cerebral blood images was done as described above for images of glucose metabolism.

Voxel-based mapping analysis. Voxel-based mapping analysis was done using SPM5. Spatially normalized glucose metabolism images were smoothed with 12-mm full width at half-maximum Gaussian kernel. Voxel maps of clamp effects were created by subtracting fasting images from clamp images. These subtraction images were compared between groups using T-contrasts, with and without age as covariate, with voxel-level uncorrected $P < 0.05$ and cluster-level corrected $P < 0.05$.

Statistical analyses of volume of interest data. Statistical analyses of volume-of-interest data were done using SPSS version 17.0 for Windows (SPSS, Chicago, IL). Data were analyzed using repeated-measures ANOVA with region, hemisphere, and condition as within-subject factors; group status as the between-subject factor; and sex as a covariate. We also ran the same model with age as a covariate. We also used paired *t* tests within groups and independent-samples *t* tests between groups. Data are mean ± SD.

RESULTS

Brain glucose metabolism. In the fasting condition, brain glucose metabolism was similar between patients with impaired glucose metabolism (whole brain: 15.6 μmol · 100 g^{-1} · min^{-1}) and healthy subjects (whole brain: 15.0 μmol · 100 g^{-1} · min^{-1}; +0.5%, $P = 0.896$).

Across all subjects, the hyperinsulinemic clamp increased whole-brain glucose metabolism by ~12% (main effect of the condition: $F = 7.11$, $P = 0.015$). However, groups were different in terms of the treatment effects (group × condition interaction: $F = 8.59$, $P = 0.009$). The hyperinsulinemic clamp increased brain glucose metabolism only in patients with impaired glucose tolerance (whole brain: +18%, $P = 0.001$) but not in healthy subjects (whole brain: +3.9%, $P = 0.373$) (Fig. 1; Table 2). This finding was confirmed by the voxel-based mapping analysis, which showed a large significant cluster throughout the brain, with the largest increase in glucose metabolism in the right posterior insula (Fig. 2). Although plasma insulin was higher in patients than in healthy subjects, fasting ($r = 0.35$, $P = 0.114$) or clamp ($r = 0.05$, $P = 0.842$) insulin, or the change from fasting to clamp ($r = -0.06$, $P = 0.792$) insulin, did not correlate with change in brain glucose metabolism.

Because the patients with impaired glucose tolerance tended to be somewhat older than healthy subjects (Table 1), we repeated the overall analysis with age as a covariate. This diminished the overall group × condition interaction ($F = 3.31$, $P = 0.085$); yet, significant regional interactions were seen in the medial temporal cortex ($F = 5.08$, $P = 0.037$) and the insula ($F = 4.78$, $P = 0.042$). Also, the voxel-based mapping analysis revealed a significant group difference in the insulin-induced change in brain glucose metabolism even with age as a covariate ($T_{max} = 4.88$ at [36, −48, −10], $k_E = 34{,}686$ voxels, cluster-level corrected $P < 0.001$). This suggests that the phenotype of impaired glucose tolerance explains the variance in the insulin-stimulated increase in brain glucose metabolism even when the effects of age are accounted for.

Cerebral blood flow. In the fasting condition, cerebral blood flow was similar between patients with impaired glucose tolerance ($n = 6$; whole brain: 40.4 mL · 100 g^{-1} · min^{-1}) and healthy subjects ($n = 8$; whole brain: 41.7 mL · 100 g^{-1} · min^{-1}; −3.1%, $P = 0.781$). The hyperinsulinemic clamp did not change cerebral blood flow either in patients with impaired glucose tolerance (whole brain: −2.7%, $P = 0.448$) or in healthy subjects (whole brain: −4.0%, $P = 0.346$).

DISCUSSION

We found that insulin stimulates brain glucose metabolism, but this effect depends on the glucose tolerance of the subjects: insulin did not increase brain glucose metabolism in subjects with normal glucose tolerance but significantly increased glucose metabolism in patients with impaired glucose tolerance. That is, the effect of insulin on brain glucose metabolism was not maximal in the fasting state in patients with impaired glucose tolerance, although it was so in healthy subjects, suggesting that the groups are differentially placed on the insulin dose-response curve.

How are these seemingly unexpected results interpreted in the context of the concept of insulin resistance? With regard to healthy subjects, our results are consistent with previous studies that have shown no effects of physiological postprandial insulin levels on brain glucose metabolism (10,11). Thus, the effect of insulin on brain glucose metabolism is already maximal at physiological fasting insulin levels in healthy subjects, because decreasing insulin levels is able to decrease brain glucose metabolism (12,13). However, insulin-resistant patients are insensitive

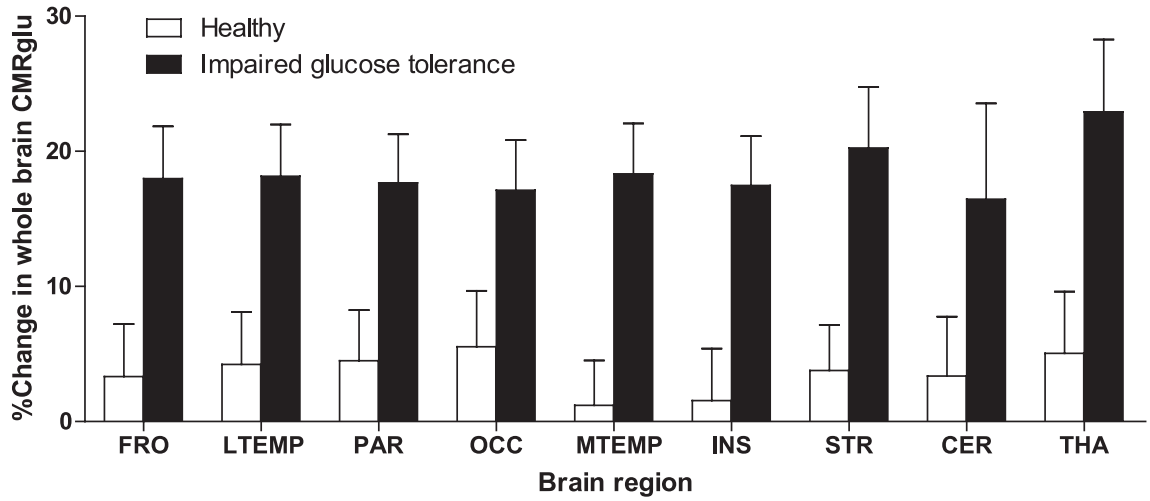

FIG. 1. The percentage of the insulin-stimulated increase in brain glucose metabolism is higher in subjects with impaired glucose tolerance. The increase in brain glucose metabolism in patients with impaired glucose tolerance was similar across brain regions, ranging from 16% in the cerebellum to 23% in the thalamus. Error bars represent the SEM.

to decreasing insulin levels (12), whereas we found higher brain responses to insulin in these patients. These findings suggest that patients with peripheral insulin resistance need more insulin than healthy subjects to get the maximal effect of insulin on brain glucose metabolism. In the fasting condition, we did not find lower glucose metabolism in patients with impaired glucose tolerance, which argues against simple insulin resistance in the brain. However, similar glucose metabolism was maintained with higher plasma insulin levels (Table 1), although the implications of this observation are unclear, given that decreasing plasma insulin does not decrease brain glucose metabolism in these patients (12).

Disturbances in brain insulin signaling in patients with impaired glucose tolerance may occur at multiple levels, including delivery of insulin in the brain across the blood-brain barrier, actions of insulin at insulin receptors, and downstream effects via second-messenger systems (4). Obese patients have a lower cerebrospinal fluid–to–plasma insulin ratio (6), which would suggest deficient delivery of insulin into the brain. However, obese patients also show decreased catabolic, but not cognitive, responses to intranasal insulin, which bypasses the blood-brain barrier (7), suggesting that insulin resistance in the brain occurs at multiple levels. Based on the current results, it may be speculated that some components along the insulin pathway in the brain are actually sensitized because of long-term deprivation of insulin stimulation and show exaggerated responses to high insulin levels in these patients. For example, if decreased insulin delivery across the blood-brain barrier and decreased responsiveness of insulin receptors inhibit stimulation of the insulin pathway at physiological insulin levels, despite compensatory hyperinsulinemia, we might expect to see increased responses to insulin when insulin levels are sufficiently high to overcome these deficits upstream in the signaling pathway. Unfortunately, no evidence for sensitization of any of the components in this signaling pathway exists in humans, and this hypothesis remains speculative until further data emerge.

TABLE 2
Regional brain glucose metabolism values in the fasting and clamp conditions in healthy subjects and in patients with impaired glucose tolerance

	Healthy subjects (n = 9)				Impaired glucose tolerance (n = 13)				Group × condition interaction
	Brain glucose metabolism (μmol · 100 g^{-1} · min^{-1})		Change		Brain glucose metabolism (μmol · 100 g^{-1} · min^{-1})		Change		
Region	Fast	Clamp	%	P	Fast	Clamp	%	P	P
FRO	15.9 ± 1.2	16.4 ± 1.5	3.3	0.506	15.8 ± 2.1	18.6 ± 2.5	18.0	**<0.001**	**0.009**
LTEMP	16.5 ± 1.2	17.2 ± 1.7	4.2	0.364	16.0 ± 1.8	18.8 ± 2.2	18.2	**<0.001**	**0.010**
PAR	14.0 ± 0.8	14.6 ± 1.6	4.5	0.283	14.7 ± 1.9	17.2 ± 2.5	17.7	**<0.001**	**0.009**
OCC	16.7 ± 0.9	17.6 ± 2.2	5.5	0.231	17.8 ± 2.2	20.7 ± 2.9	17.1	**<0.001**	**0.015**
MTEMP	12.8 ± 0.6	12.9 ± 1.1	1.2	0.778	13.0 ± 1.6	15.3 ± 1.9	18.3	**<0.001**	**0.003**
INS	17.5 ± 1.2	17.7 ± 1.7	1.6	0.777	16.3 ± 1.9	19.0 ± 2.0	17.5	**<0.001**	**0.003**
STR	16.9 ± 0.9	17.5 ± 1.6	3.8	0.340	16.2 ± 2.3	19.2 ± 2.2	20.2	**<0.001**	**0.013**
CER	10.6 ± 1.2	10.9 ± 1.5	3.4	0.529	10.7 ± 1.9	12.2 ± 2.0	16.5	**0.035**	0.150
THA	16.4 ± 1.6	17.1 ± 2.3	5.0	0.327	16.2 ± 2.9	19.5 ± 2.6	22.9	**<0.001**	**0.020**

P values are from paired samples t tests except for the last column, where P values are from the group × condition interaction in repeated-measures ANOVA. P values denoting statistical significance ($P < 0.05$) appear in boldface. CER, cerebellum; FRO, frontal cortex; INS, insula; LTEMP, lateral temporal cortex; MTEMP, mesial temporal cortex; OCC, occipital cortex; PAR, parietal cortex; STR, striatum; THA, thalamus.

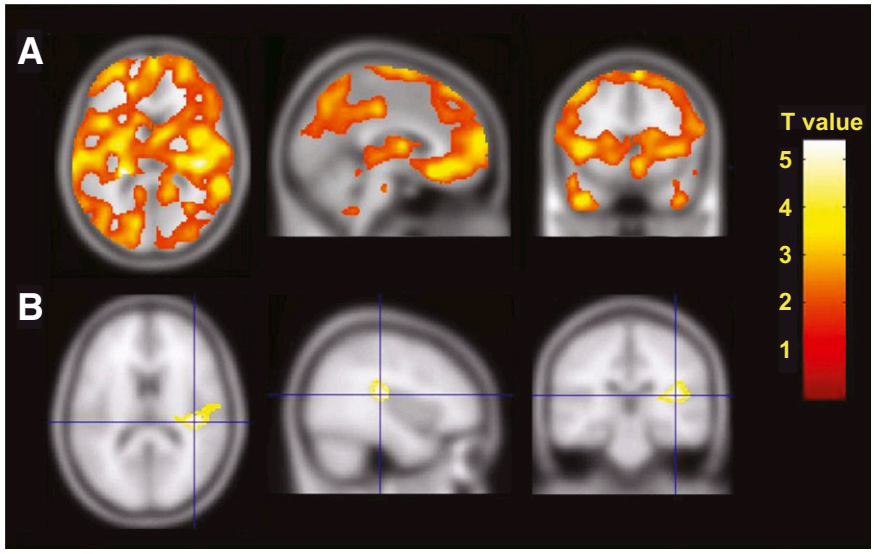

FIG. 2. Results from the voxel-based statistical parametric mapping analysis, demonstrating a higher insulin-stimulated increase in brain glucose metabolism in subjects with impaired glucose tolerance than in healthy subjects. *A*: An exploratory analysis with voxel-level uncorrected $P < 0.05$ revealed a large cluster that encompasses most gray matter regions in the brain. *B*: Stricter analysis with voxel-level uncorrected $P < 0.001$ demonstrating the most significant difference localized in the right posterior insula ($T_{max} = 5.39$ at [40, −26, 14], $k_E = 116{,}567$ voxels, cluster-level corrected $P < 0.001$). Color scale represents the T value at the voxel level.

We measured brain glucose metabolism using the macroparameter CMRglu and cannot therefore distinguish between increased glucose transport across the blood-brain barrier and increased brain hexokinase activity in patients with impaired glucose tolerance. Similarly, we cannot distinguish whether the effects of insulin on brain glucose metabolism are direct by stimulation of glucose metabolism, or indirect by stimulation of neuronal activity via neurotransmitter activity. Because our PET measurements with [^{15}O]H_2O showed no effects of insulin on cerebral blood flow, we conclude that insulin does not increase brain delivery of glucose simply by increased cerebral blood flow. Previous studies have found decreased baseline cerebral blood flow in patients with type 1 (22) and type 2 (23) diabetes, likely representing microvascular damage from chronic hyperglycemia. We did not find such alterations in patients with impaired glucose tolerance, suggesting that microvascular damage may be minimal in this prediabetic state, insofar as biologically meaningful deficits are detected by [^{15}O]H_2O PET.

The highest insulin-stimulated increase in glucose metabolism was seen in the posterior insula, a region that monitors bodily states and is implicated in reward functions (24). A recent study (25) found increased functional responses to gastric distention in obese subjects in the posterior insula. Thus, the posterior insula may be one of the regions where insulin reduces feeding behavior in humans.

In conclusion, we used [^{18}F]FDG PET to show that insulin does not stimulate brain glucose metabolism at physiological postprandial levels in healthy subjects but does so in patients with impaired glucose tolerance. These results suggest that insulin regulation of brain glucose metabolism is disturbed in metabolic syndrome.

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J.H. researched data, contributed to discussion, and wrote the manuscript. K.A.V., L.N., J.C.H., M.-J.H., M.B., S.V.N., J.R., P.I., and P.N. researched data, contributed to discussion, and reviewed and edited the manuscript.

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