Euglycemic Infusion of Insulin Detemir Compared With Human Insulin Appears to Increase Direct Current Brain Potential Response and Reduces Food Intake While Inducing Similar Systemic Effects

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OBJECTIVE—In the treatment of diabetic patients, the long-acting insulin analog insulin detemir is less prone to induce weight gain than other insulin formulations. Assuming that because of its pharmacologic properties, detemir displays stronger central nervous anorexigenic efficacy than human insulin, we compared acute effects of human insulin and detemir on electro-encephalography (EEG) measures and food intake.

RESEARCH DESIGN AND METHODS—Frontocortical EEG direct current (DC) potentials were recorded in 15 healthy men during two hyperinsulinemic-euglycemic clamps that included an insulin bolus injection (human insulin, 17.75 mU/kg body wt; detemir, 90 mU/kg body wt) followed by a steady 90-min infusion (1.0 vs. 2.0 mU · kg^{-1} · min^{-1}). A higher dosage was chosen for detemir to compensate for its delay in impact relative to human insulin and to elicit similar systemic effects. At 20 min after infusion, subjects were allowed to eat ad libitum from a test buffet.

RESULTS—Mean glucose infusions to maintain euglycemia ($P > 0.93$) and blood glucose concentrations ($P > 0.34$) did not differ between conditions. Detemir infusion induced a negative DC-potential shift, averaging -372.2 μV from 21 to 90 min that was not observed during human insulin infusion (146.5 μV, $P = 0.02$). Detemir, in comparison with human insulin, reduced subsequent food intake by 303 kcal (1,257 vs. 1,560, $P < 0.04$).

CONCLUSIONS—While inducing comparable peripheral effects, detemir exerts stronger acute effects on brain functions than human insulin and triggers a relative decrease in food consumption, suggesting an enhanced anorexigenic impact of detemir compared with human insulin on central nervous networks that control nutrient uptake. *Diabetes* 59:1101–1107, 2010

Systemic insulin accessing the brain via an active, saturable transport mechanism (1) is assumed to contribute to the central nervous regulation of energy homeostasis (2). Experimental administration of insulin to the central nervous system inhibits food intake and reduces body fat content in animals (3,4) and humans (5,6), suggesting that circulating insulin provides negative, anorexigenic feedback on the amount of body fat to the brain. The long-acting insulin analog insulin detemir, because of the acylation of a 14-carbon fatty acid (myristic acid) to lysine at locus B29, displays increased self-association and reversible albumin binding (7,8), which delays absorption of the molecule and thereby reduces the risk of hypoglycemic episodes (9,10). Insulin therapy using detemir has been frequently found to induce weight-sparing effects in comparison with other insulins, curtailing body weight gain in patients with type 2 diabetes (11,12) and maintaining stable body weight in type 1 diabetic patients (9,13,14). The mechanisms behind this favorable effect of detemir are unclear. Because of its pharmacologic properties, detemir might cross the blood-brain barrier faster and in higher quantities than other insulins and induce stronger effects on brain functions (15,16). Supporting this assumption, detemir in comparison with human insulin has been found to amplify the central nervous impact of hypoglycemia (16,17) and to exert stronger magnetoencephalographic effects in overweight humans (15) who display relative central nervous insulin resistance (18–20). To investigate the relevance of enhanced central nervous detemir action in the regulation of food intake, we assessed the effects of euglycemic intravenous infusion of detemir in comparison with human insulin on electroencephalography (EEG) direct current (DC) potentials that are sensitive to changes in systemic insulin concentrations (21) as well as on free-choice food intake. As we aimed at comparing the brain impact of peripherally equipotent doses of detemir and human insulin, care was taken for both infusions to induce similar effects on systemic glucose homeostasis.

RESEARCH DESIGN AND METHODS

Subjects and design. According to a single-blind, within-subject comparison, 15 healthy, normal-weight men (mean age ± SE, 28.5 ± 1.0 years; BMI, 23.1 ± 0.5 kg/m²) participated in two hyperinsulinemic-euglycemic clamp experiments (human insulin, detemir) spaced apart at least 1 week. The order of conditions was balanced across subjects. All subjects gave written informed consent to the experiments, which were approved by the local ethics committee. In both experimental conditions, an insulin bolus injection (17.75

TABLE 1
Composition of the test buffet

Food	Weight (g)	Energy (kcal)	Carbohydrate (g)	Fat (g)	Protein (g)
Bread rolls	300	719	153	4	8
Whole-grain bread	165	372	71	2	12
White bread	30	75	15	0.40	2
Butter	100	773	0.60	83	0.67
Jam	50	152	36	0.08	0.03
Honey	40	127	30	0	0.14
Hazelnut spread	40	142	30	0.32	3
Poultry sausage	40	75	0.13	4	8
Salami sausage	34	120	0.07	10	6
Semihard cheese	100	377	0.00	29	26
Spread cheese	33	87	0.63	8	3
Cream cheese	40	124	1	12	3
Fruit curd	150	173	23	4	9
Vanilla pudding	125	137	21	4	4
Apple	130	72	15	0.78	0.39
Banana	150	146	32	0.30	2
Whole milk	750	499	36	26	25
Strawberry milk	200	171	18	7	7
Orange juice	400	178	36	1	4
Condensed milk	30	34	3	1	2
Sugar	24	101	24	0	0
Total		4,654	545	197	125

Composition of the buffet offered 20 min after infusion of human insulin and insulin detemir, respectively, had been stopped and from which subjects were allowed to eat ad libitum for 50 min. The buffet was served with coffee or tea. All values higher than 1 are rounded.

mU/kg body wt [= 0.1065 nmol/kg body wt] human insulin, Insulin Actrapid; Novo Nordisk, Bagsværd, Denmark; 90 mU/kg body wt [= 2.16 nmol/kg body wt] detemir, Insulin Levemir; Novo Nordisk) was given followed by a steady 90-min infusion of 1.0 mU $\cdot$ kg^{-1} $\cdot$ min^{-1} (= 0.006 nmol $\cdot$ kg^{-1} $\cdot$ min^{-1}) human insulin versus 2.0 mU $\cdot$ kg^{-1} $\cdot$ min^{-1} (= 0.048 nmol $\cdot$ kg^{-1} $\cdot$ min^{-1}) detemir. To compensate for the relatively slower onset of the action of detemir, a higher dosage was chosen (15,17) to induce comparable peripheral effects of both compounds as assessed by rates of glucose infusion necessary to keep blood glucose levels in the euglycemic range.

Procedure. Volunteers reported to the laboratory at 0800, after an overnight fast of 10 h, and were prepared for electroencephalographic recordings, insulin infusions, and blood samplings. We inserted venous cannulas into the subject's arms and connected them to tubes enabling infusion and blood sampling from an adjacent room without awareness of the subject. The arm from which samples were taken was positioned in a heated box (55°C) to enable drawing of arterialized venous blood. During recordings, subjects sat in a reclining chair in a sound-attenuated room of constant temperature, with their heads stabilized by a cushion. They were instructed to relax and not to move during recordings and to fixate their gaze on the wall in front of them. Subjects pressed a button every estimated 30 s to maintain a constant state of mental activity and to not doze off.

Recordings of DC potentials started at 0940 with a baseline phase of 20 min followed by the bolus injection of human insulin and detemir, respectively ($t = 0$). Subsequent insulin infusion lasted for 90 min, ending at 1130 when EEG recordings were also stopped. Arterialized blood was drawn at 15-min intervals during baseline, at 5-min intervals during insulin infusion, and at ~15-min intervals thereafter to monitor blood glucose concentration (HemoCue B-Glucose-Analyzer, HemoCue AB, Angelholm, Sweden). During and after insulin administration, subjects intravenously received a 20% glucose solution at a variable rate to maintain normal plasma glucose levels. Blood samples for the determination of hormonal parameters were repeatedly collected, and routine assays were used to determine concentrations of serum C-peptide, plasma ACTH, serum cortisol (all Immulite; DPC, Los Angeles, CA), plasma glucagon (RIA; Adaltis, Montreal, Quebec, Canada), and serum leptin (RIA; Linco Research, St. Charles, MO).

Food intake and mood assessment. At 1150 (i.e., 20 min after insulin infusion had stopped), a standardized buffet of around 4,650 kcal was offered from which subjects were allowed to eat ad libitum during the subsequent 50 min (Table 1). Subjects were kept unaware of hypothesized treatment effects on food intake and were not aware that their food intake was measured by weighing buffet components before and after food intake. In addition, to prevent overeating, subjects were allowed to take with them any remaining food afterward. Before (at 0915) and after (at 1135) recordings and at the end of the session at ~1300, subjects rated their hunger, thirst, and tiredness on

10-point scales and completed a questionnaire assessing alertness and autonomic symptoms on 5-point bipolar scales of 20 contrasting adjective pairs (e.g., activated-inert and sweating-shivery) (22). They also filled in a checklist of 161 adjectives assessing mood on 14 dimensions (23).

Recordings. Standard recordings of DC potentials, electro-oculogram, and electromyogram were performed as described previously (24,25). DC-potential recordings were obtained from left and right frontal (F3, F4), frontocentral (FC3, FC4), and central (C3, C4) electrodes referenced to linked electrodes at the mastoids. A BrainAmp DC amplifier (Brain Vision, London, U.K.; low-pass filter: 30 Hz, sampling rate: 200 Hz) was used. DC-potential drifts with short-circuited input were constantly <5 μV/h, and electrode impedance, measured before and after recordings, never exceeded 5 kΩ. Average DC-potential values were determined offline for subsequent 5-s intervals. Linear potential drifts during the 20-min baseline period extending into the 90-min insulin infusion period were removed using a linear regression method. Periods where electromyogram or electro-oculogram indicated increased muscular activity or eye movements were excluded from analysis. The average DC potential during baseline was set to 0 μV, and potential shifts during treatment were expressed as difference values.

Statistical analysis. Differences in DC-potential values between conditions were evaluated first on an exploratory basis by point-wise comparisons using t tests to identify time ranges with most consistent differences (26). The time range selected for analysis covered 21–90 min of insulin infusion. Values for this time interval were then subjected to ANOVA, including the repeated-measures factors Treatment (human insulin vs. detemir) and Topography (electrode locations). Degrees of freedom were corrected using the Greenhouse-Geisser procedure. Post hoc contrasts were used to specify significant ANOVA main effects and interactions. For the DC-potential analysis, data from four subjects had to be excluded because of technical failures and artifacts of apparent nonbiological origin. Behavioral measures and hormonal parameters were analyzed with ANOVA and paired t tests as appropriate. $P \leq 0.05$ was considered significant.

RESULTS

Glucose infusion rates, blood glucose, and hormonal parameters. Rates of glucose infusion to maintain eugly-cemia were similar between conditions (Fig. 1A; $P > 0.14$ for all comparisons), resulting in identical total amounts of energy supplied via glucose infusion (human insulin, 240.8 ± 23.3 kcal; detemir, 239.5 ± 25.0 kcal; $P > 0.93$). Correspondingly, blood glucose concentrations were com-
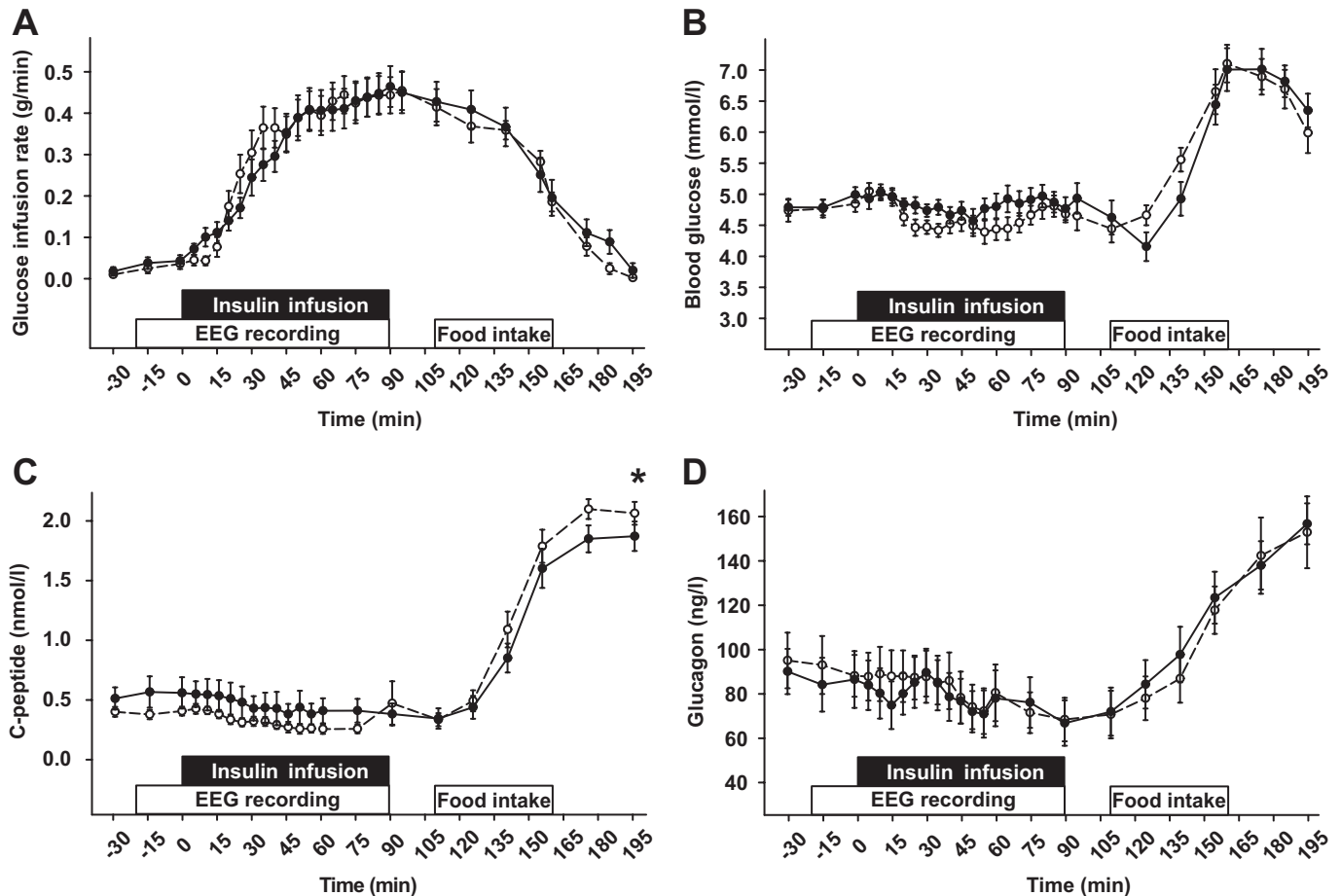
FIG. 1. *A*: Rates of glucose infused to maintain euglycemia and concentrations of (*B*) blood glucose, (*C*) serum C-peptide, and (*D*) serum glucagon during intravenous infusion of human insulin (○) and insulin detemir (●), respectively. Infusions started with an insulin bolus injection (human insulin, 17.75 mU/kg body wt; detemir, 90 mU/kg body wt) followed by a steady 90-min infusion (1.0 vs. 2.0 mU · kg^{-1} · min^{-1}). At 20 min after the end of infusions, subjects ate ad libitum from a test buffet. *$P < 0.05$ for comparisons between conditions (*t* test). *n* = 15.

parable throughout the experiment (Fig. 1*B*; $P > 0.34$ for all comparisons) as well as when restricting analysis to the period of insulin infusion ($P > 0.13$). Serum C-peptide concentrations did not differ between conditions during insulin infusion ($P > 0.25$) but rose to slightly elevated levels in the human insulin compared with the detemir condition at the end of experiments (Fig. 1*C*; F[3,46] = 3.77, $P < 0.02$ for Treatment × Time). Concentrations of serum glucagon (Fig. 1*D*) as well as leptin did not differ between conditions (all comparisons, $P > 0.40$). Concentrations of plasma ACTH ($P > 0.57$) and serum cortisol ($P > 0.71$) were likewise similar in both conditions, with cortisol levels showing the expected meal-related increase (F[3,47] = 4.19, $P < 0.008$).

Negative DC-potential shift during detemir infusion. The DC potential in the detemir condition showed a marked negative shift shortly after insulin injection that reached maximum values exceeding −600 μV toward the end of the recording epoch (Fig. 2). This strong negative DC shift was generally absent in the human insulin condition. Analyses of average DC-potential levels during the relevant interval from 21 min after the start until the end of insulin infusions confirmed a distinctly more negative potential level in the detemir than human insulin condition (F[1,10] = 7.03, $P = 0.02$; Table 2), with this effect displaying an even topographic distribution (F[2,24] = 0.59, $P > 0.59$, for Treatment × Electrode location). Comparisons with preinjection baseline levels confirmed

significance for the negative DC potential in the detemir condition during 21–90 min of insulin infusion (F[1,10] = 8.53, $P = 0.02$; F[3,27] = 1.04, $P > 0.39$ for Electrode location). Although DC potentials in the human insulin condition appeared to shift slightly toward positive values over central positions, respective analyses did not yield significant differences from baseline values (F[1,10] = 0.17, $P > 0.43$; Table 2).

Reduction of food intake by detemir in comparison with human insulin. Table 3 summarizes treatment effects on food intake. Detemir in comparison with human insulin significantly reduced food consumption by 303 ± 135.7 kcal. Macronutrient comparisons suggested this effect was particularly pronounced for protein and, to a lesser extent, for carbohydrate intake, but there was no significant statistical interaction between the factors Treatment and Macronutrients (F[2,24] = 1.63, $P > 0.22$). The reduction in total energy consumption and also carbohydrate intake by detemir in comparison with human insulin was also observed in analyses taking into account the energy received in the form of intravenous glucose (Table 3). Differences in carbohydrate and protein intake between conditions correlated significantly with respective differences in DC-potential shifts (averaged over all recording sites) from 21 to 90 min of infusions ($r = 0.74$, $P < 0.04$, and $r = 0.87$, $P < 0.01$, respectively, bivariate Pearson coefficients). The respective correlation with total
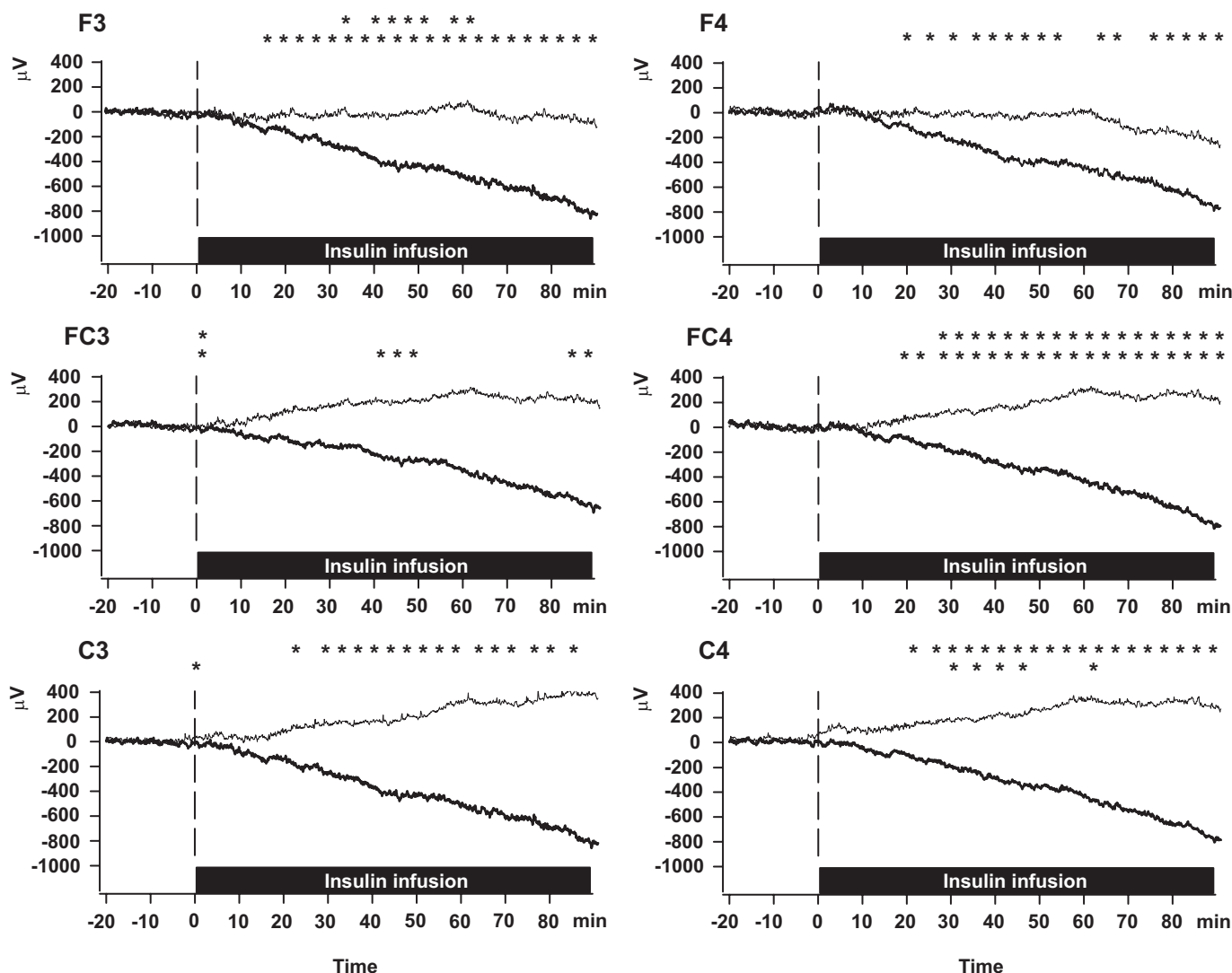
FIG. 2. Average DC potentials recorded from left and right electrodes over frontal (F3, F4, respectively), frontocentral (FC3, FC4), and central (C3, C4) cortical areas before and during intravenous infusion of human insulin (*thin lines*) and insulin detemir (*bold lines*), respectively. Infusions started with an insulin bolus injection (human insulin, 17.75 mU/kg body wt; detemir, 90 mU/kg body wt) followed by a steady 90-min infusion (1.0 vs. 2.0 mU · kg⁻¹ · min⁻¹). In both conditions, euglycemia was maintained by infusion of glucose. The average potential during baseline was set to 0 μV. Rows of asterisks indicate significance ($P < 0.05$; t tests) for point-wise comparisons of the potential levels between conditions (*upper row*) and between the detemir condition and respective baseline levels (*lower row*). $n = 11$.

energy intake failed to reach significance ($r = 0.61$, $P = 0.11$; $r = 0.21$, $P > 0.62$ for fat intake).

Rating scales. Ten-point scale hunger ratings did not differ between conditions, showing the expected decline

from baseline (detemir, 4.87 ± 0.68; human insulin, 5.93 ± 0.54; $P > 0.11$) and post-EEG recording values (5.87 ± 0.62 vs. 5.93 ± 0.56, $P > 0.91$) to low postingestion levels (1.47 ± 0.43 vs. 1.00 ± 0.24, $P > 0.33$; $P > 0.12$ for

TABLE 2
DC-potential levels during euglycemic infusion of human insulin and detemir

Site	HI (mean ± SE)	Det (mean ± SE)	HI vs. Det (P value)	HI vs. baseline (P value)	Det vs. baseline (P value)
F3	−7.19 ± 168.77	−470.24 ± 148.92	0.06	0.97	**0.01**
FC3	211.28 ± 243.76	−343.87 ± 169.76	0.13	0.41	0.07
C3	261.43 ± 161.82	−161.39 ± 114.50	**0.03**	0.14	0.19
F4	−61.82 ± 224.03	−426.24 ± 179.60	0.25	0.79	**0.04**
FC4	213.07 ± 239.50	−406.36 ± 139.26	**0.01**	0.39	**0.02**
C4	262.01 ± 125.39	−425.00 ± 202.89	**0.01**	0.06	0.06

Average DC-potential levels (in μV) over left and right frontal (F3, F4), frontocentral (FC3, FC4), and central (C3, C4) cortical areas from 21 to 90 min of intravenous infusion of human insulin (HI) and insulin detemir (Det), respectively. Plasma glucose levels were held constant by additional glucose infusion. DC-potential values indicate differences from baseline (set to 0 μV). The right three columns indicate significance for differences, respectively, between conditions and between the potential levels in the human insulin and detemir conditions and respective baseline levels (t test; $n = 11$). Bold indicates statistical significance.

TABLE 3
Food intake after euglycemic infusion of human insulin and detemir

	Human insulin (mean $\pm$ SE)	Detemir (mean $\pm$ SE)	P value
Total intake (kcal)	1,559.79 $\pm$ 138.72	1,256.78 $\pm$ 82.41	**0.04**
Carbohydrate (kcal)	803.18 $\pm$ 50.59	630.14 $\pm$ 49.76	0.06
Fat (kcal)	554.53 $\pm$ 83.70	472.32 $\pm$ 61.31	0.20
Protein (kcal)	202.09 $\pm$ 20.40	154.32 $\pm$ 13.41	**0.004**
Carbohydrate (% of total intake)	53.99 $\pm$ 3.20	51.39 $\pm$ 3.37	0.40
Fat (% of total intake)	33.19 $\pm$ 2.91	36.25 $\pm$ 3.24	0.32
Protein (% of total intake)	12.82 $\pm$ 0.49	12.36 $\pm$ 0.70	0.53
Total intake (including glucose infusion; kcal)	1,782.81 $\pm$ 133.73	1,475.34 $\pm$ 79.49	**0.04**
Carbohydrate (including glucose infusion; kcal)	1,026.20 $\pm$ 54.28	848.69 $\pm$ 52.50	**0.05**

Food intake from a test buffet of 4,650 kcal offered 20 min after infusion of human insulin and insulin detemir, respectively, had been stopped and from which subjects were allowed to eat ad libitum for 50 min. Bottom lines indicate food consumption including the amount of energy infused as glucose to maintain euglycemia until the end of the test buffet. Right column indicates significance for differences between conditions (t test; $n = 15$). Bold indicates statistical significance.

Treatment $\times$ Time). A comparable pattern without significant differences between conditions was observed for thirst (all $P > 0.12$) and tiredness ($P > 0.33$) ratings. According to the bipolar questionnaire, subjects in the detemir compared with the human insulin condition felt more critical (critical-comfortable, 2.87 $\pm$ 0.13 vs. 3.27 $\pm$ 0.18, $P < 0.009$) and reported increased wakefulness (sleepy-awake, 3.33 $\pm$ 0.23 vs. 2.73 $\pm$ 0.23, $P < 0.03$) and hunger (full-hungry, 4.20 $\pm$ 0.20 vs. 3.53 $\pm$ 0.22, $P < 0.01$) immediately after infusions. The remaining dimensions and the post–food intake assessment were not affected. The mood adjective checklist did not yield significant differences between conditions for any of the subscales.

DISCUSSION

Administration of insulin to the central nervous system reduces food intake (3,5) and body weight (4,6). We demonstrate that while eliciting comparable peripheral effects, euglycemic infusion of insulin detemir compared with human insulin triggers a distinct negative shift in EEG DC-potential recordings and reduces calorie uptake in healthy men, supporting our hypothesis that detemir affects brain functions to a greater extent than human insulin and induces stronger anorexigenic effects on central nervous networks that control food intake. This outcome suggests that enhanced catabolic insulin signaling to the brain may be an important mechanism behind the limitation of weight gain observed in diabetic patients receiving detemir treatment (9,11–14).

In accordance with other investigators (15,17), we administered insulin doses that were considerably higher in the detemir than in the human insulin condition to compensate for the delayed onset that human insulin–equimolar detemir dosages would display. Accordingly, timing and strength of the effects of detemir and human insulin on systemic glucose homeostasis as reflected by the rates of glucose infusion as well as blood glucose and serum glucagon concentrations were identical. C-peptide concentrations likewise did not differ between conditions during insulin infusion, merely showing a slight increase in the human insulin condition after the test buffet that may have been due to greater food intake in this compared with the detemir condition. Congruent peripheral effects were also indicated by comparable serum leptin concentrations that are known to respond to insulin infusion (27,28).

On the background of equipotent systemic effects, detemir elicited a marked brain response as indicated by a widespread negative shift of scalp-recorded DC potentials that started around 15 min after detemir bolus injection and exceeded potential levels in the control condition that remained unaffected by human insulin infusion. In the human insulin condition, subjects received roughly the same total amount of insulin that, when administered in single bolus form, induced a negative DC-potential shift in foregoing experiments (21). Slowly infused over the course of 90 min, this dose obviously was too weak a stimulus to evoke DC-potential responses to human insulin in the present experiments. In contrast, the 90-min infusion of a detemir dose equivalent in terms of systemic action triggered a sustained negative DC-potential shift comparable with the previously reported effect of human insulin administered in high-dose bolus form (21). This pattern indicates that although central nervous detemir effects may be mimicked by disproportionally high doses of human insulin, the relative impact of detemir on brain functions is considerably greater when both insulins are administered at doses with similar peripheral impact.

The mechanisms behind the strong effect of detemir on scalp-recorded DC potentials cannot be derived from our data. Brain DC-potential shifts of this amplitude most likely reflect changes in extracellular ionic concentrations stemming from potential shifts at glial membranes that are endowed with receptors for insulin and IGF (21,29–31). The assumption of a widespread effect on cerebral cellular networks also fits with the global nature and long duration of the DC-potential shifts induced by detemir infusion. Our observations corroborate previous findings of increased brain responses to detemir in comparison with human insulin in animals (32) and humans (15–17). Superior central nervous efficacy of detemir may be due to improved permeation of the lipophilic molecule into the brain compartment, with enhanced receptor-mediated blood-brain barrier transport of albumin-bound detemir adding to this effect (15,32). The detemir-induced negative DC-potential shift that is presumably of primary glial origin thus may be reinforced by electrical potentials generated in the course of receptor-mediated detemir transport across the blood-brain barrier (33).

A most remarkable finding of our study is the reduction of ad libitum food intake by around 300 kcal in the detemir compared with the human insulin condition in the presence of identical peripheral actions of both insulins. This pattern renders the contribution of systemic mediators to this effect highly unlikely, rather suggesting that enhanced

central nervous insulin signaling in the detemir condition resulted in decreased caloric intake. The concept of insulin providing catabolic feedback on the body's energy resources to brain networks that control energy homeostasis has been well established in animals (2,3) as well as in humans (5,6). Thus, the decrease in food intake after detemir compared with human insulin infusion suggests that the enhanced effect on brain functions indicated by the negative DC-potential shift particularly impacts the central nervous control of food intake. Although because of methodological constraints, DC-EEG could not be recorded during food intake proper (34), this interpretation is supported by the strong correlation between the reduction in calorie intake and the antecedent DC-potential effect elicited by detemir. It is also in line with animal experiments in which intravenous detemir compared with human insulin injections were associated with enhanced insulin receptor phosphorylation in hypothalamic and cerebrocortical tissue in conjunction with increased EEG-assessed cortical activity, whereas the activation of the insulin receptor signaling cascade was similar in muscle tissue and liver (32). Interestingly, detemir compared with human insulin infusion increased rather than decreased self-rated hunger before test buffet presentation, which may have been due to a biasing influence of enhanced wakefulness and activation after detemir infusion (35). Alternatively, this finding may also indicate that central nervous insulin exerts its anorexigenic effects via meal-related signals that contribute to the termination of a meal, but not by affecting hunger motivation per se (5).

Weight gain is a frequent side effect when blood glucose levels of diabetic patients are normalized by insulin (36,37), but is less pronounced in patients undergoing detemir therapy (9,11–14). The assumption that the use of detemir limits weight gain because its favorable safety profile decreases defensive snacking to prevent hypoglycemia was not supported by comparative clinical studies showing that insulin glargine, which like detemir reduces the risk of hypoglycemia, is associated with greater weight gain than detemir (38,39). Against this background, the anorexigenic brain impact of detemir found in our study rather suggests the contribution of central nervous mechanisms to the weight-sparing effect of detemir in the clinical context.

REFERENCES

1. Woods SC, Seeley RJ, Baskin DG, Schwartz MW. Insulin and the blood-brain barrier. Curr Pharm Des 2003;9:795–800
2. Morton GJ, Cummings DE, Baskin DG, Barsh GS, Schwartz MW. Central nervous system control of food intake and body weight. Nature 2006;443:289–295
3. Woods SC, Lotter EC, McKay LD, Porte D Jr. Chronic intracerebroventricular infusion of insulin reduces food intake and body weight of baboons. Nature 1979;282:503–505
4. Clegg DJ, Riedy CA, Smith KA, Benoit SC, Woods SC. Differential sensitivity to central leptin and insulin in male and female rats. Diabetes 2003;52:682–687
5. Benedict C, Kern W, Schultes B, Born J, Hallschmid M. Differential sensitivity of men and women to anorexigenic and memory-improving effects of intranasal insulin. J Clin Endocrinol Metab 2008;93:1339–1344
6. Hallschmid M, Benedict C, Schultes B, Fehm HL, Born J, Kern W. Intranasal insulin reduces body fat in men but not in women. Diabetes 2004;53:3024–3029
7. Kurtzhals P. Engineering predictability and protraction in a basal insulin analogue: the pharmacology of insulin detemir. Int J Obes Relat Metab Disord 2004;28(Suppl. 2):S23–S28
8. Kurtzhals P, Schäffer L, Sørensen A, Kristensen C, Jonassen I, Schmid C, Trüb T. Correlations of receptor binding and metabolic and mitogenic potencies of insulin analogs designed for clinical use. Diabetes 2000;49:999–1005
9. De Leeuw I, Vague P, Selam JL, Skeie S, Lang H, Draeger E, Elte JW. Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NPH insulin. Diabetes Obes Metab 2005;7:73–82
10. Heise T, Nosek L, Rønn BB, Endahl L, Heinemann L, Kapitza C, Draeger E. Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. Diabetes 2004;53:1614–1620
11. Hermansen K, Davies M, Derezinski T, Martinez Ravn G, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetes Care 2006;29:1269–1274
12. Raslovà K, Bogoev M, Raz I, Leth G, Gall MA, Hâncu N. Insulin detemir and insulin aspart: a promising basal-bolus regimen for type 2 diabetes. Diabetes Res Clin Pract 2004;66:193–201
13. Home P, Bartley P, Russell-Jones D, Hanaire-Broutin H, Heeg JE, Abrams P, Landin-Olsson M, Hylleberg B, Lang H, Draeger E, Study to Evaluate the Administration of Detemir Insulin Efficacy, Safety and Suitability (STEADINESS) Study Group. Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes: a randomized clinical trial. Diabetes Care 2004;27:1081–1087
14. Hermansen K, Fontaine P, Kukolja KK, Peterkova V, Leth G, Gall MA. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. Diabetologia 2004;47:622–629
15. Tschritter O, Hennige AM, Preissl H, Porubska K, Schafer SA, Lutzenberger W, Machicao F, Birbaumer N, Fritsche A, Haring HU. Cerebrocortical beta activity in overweight humans responds to insulin detemir. PLoS One 2007;2:e1196
16. Rossetti P, Porcellati F, Ricci NB, Candeloro P, Cioli P, Bolli GB, Fanelli CG. Different brain responses to hypoglycemia induced by equipotent doses of the long-acting insulin analog detemir and human regular insulin in humans. Diabetes 2008;57:746–756
17. Tschritter O, Schafer SA, Klett J, Pfafflin A, Haring HU, Hennige AM, Fritsche A. Insulin detemir causes increased symptom awareness during hypoglycaemia compared to human insulin. Diabetes Obes Metab 2009;11:1017–1026
18. Tschritter O, Preissl H, Hennige AM, Stumvoll M, Porubska K, Frost R, Marx H, Klösel B, Lutzenberger W, Birbaumer N, Häring HU, Fritsche A. The cerebrocortical response to hyperinsulinemia is reduced in overweight humans: a magnetoencephalographic study. Proc Natl Acad Sci U S A 2006;103:12103–12108
19. Hallschmid M, Schultes B. Central nervous insulin resistance: a promising target in the treatment of metabolic and cognitive disorders? Diabetologia 2009;52:2264–2269
20. Hallschmid M, Benedict C, Schultes B, Born J, Kern W. Obese men respond to cognitive but not to catabolic brain insulin signaling. Int J Obes (Lond) 2008;32:275–282
21. Hallschmid M, Schultes B, Marshall L, Mölle M, Kern W, Bredthauer J, Fehm HL, Born J. Transcortical direct current potential shift reflects immediate signaling of systemic insulin to the human brain. Diabetes 2004;53:2202–2208
22. Pietrowsky R, Preuss S, Born J, Pauschinger P, Fehm HL. Effects of

cholecystokinin and calcitonin on evoked brain potentials and satiety in man. Physiol Behav 1989;46:513–519

23. Janke W, Debus G. *Die Eigenschaftswörterliste (EWL)*. Göttingen, Germany, Hogrefe, 1978

24. Marshall L, Mölle M, Fehm HL, Born J. Scalp recorded direct current brain potentials during human sleep. Eur J Neurosci 1998;10:1167–1178

25. Schmitt B, Mölle M, Marshall L, Born J. Scalp recorded direct current potential shifts associated with quenching thirst in humans. Psychophysiology 2000;37:766–776

26. Guthrie D, Buchwald JS. Significance testing of difference potentials. Psychophysiology 1991;28:240–244

27. Wellhoener P, Fruehwald-Schultes B, Kern W, Dantz D, Kerner W, Born J, Fehm HL, Peters A. Glucose metabolism rather than insulin is a main determinant of leptin secretion in humans. J Clin Endocrinol Metab 2000;85:1267–1271

28. Fruehwald-Schultes B, Oltmanns KM, Kern W, Born J, Fehm HL, Peters A. The effect of experimentally induced insulin resistance on the leptin response to hyperinsulinaemia. Int J Obes Relat Metab Disord 2002;26:510–516

29. Kum W, Zhu SQ, Ho SK, Young JD, Cockram CS. Effect of insulin on glucose and glycogen metabolism and leucine incorporation into protein in cultured mouse astrocytes. Glia 1992;6:264–268

30. Fields RD, Stevens-Graham B. New insights into neuron-glia communication. Science 2002;298:556–562

31. Heinemann U, Lux HD, Marciani MG, Hofmeier G. Slow potentials in relation to changes in extracellular potassium activity in the cortex of cats. In *Origin of Cerebral Field Potentials*. Speckmann EJ, Caspers H (Eds.). Stuttgart, Germany, Georg Thieme Publishers, 1979, p. 33–43

32. Hennige AM, Sartorius T, Tschritter O, Preissl H, Fritsche A, Ruth P, Häring HU. Tissue selectivity of insulin detemir action in vivo. Diabetologia 2006;49:1274–1282

33. Pardridge WM. Transport of insulin-related peptides and glucose across the blood-brain barrier. Ann N Y Acad Sci 1993;692:126–137

34. Schmitt B, Mölle M, Marshall L, Hallschmid M, Born J. Scalp recorded direct current (DC) potential shifts associated with food intake in hungry humans. Behav Brain Res 2001;119:85–92

35. Kern W, Peters A, Fruehwald-Schultes B, Deininger E, Born J, Fehm HL. Improving influence of insulin on cognitive functions in humans. Neuroendocrinology 2001;74:270–280

36. Russell-Jones D, Khan R. Insulin-associated weight gain in diabetes: causes, effects and coping strategies. Diabetes Obes Metab 2007;9:799–812

37. Wing RR, Klein R, Moss SE. Weight gain associated with improved glycemic control in population-based sample of subjects with type I diabetes. Diabetes Care 1990;13:1106–1109

38. Riddle MC, Rosenstock J, Gerich J, Insulin Glargine 4002 Study Investigators. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003;26:3080–3086

39. Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Schernthaner G. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetologia 2008;51:408–416