Original Article

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 electroencephalography (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 clamp conditions 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 −372.3 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

Systolic 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 peripheral 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

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Received 8 October 2009 and accepted 7 January 2010. Published ahead of print at http://diabetes.diabetesjournals.org on 12 January 2010. DOI: 10.2337/db09-1493.

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**RESULTS**

**Glucose infusion rates, blood glucose, and hormonal parameters.** Rates of glucose infusion to maintain euglycemia 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-
comparable throughout the experiment (Fig. 1B; \( P > 0.34 \) 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. 1C; \( F[3,46] = 3.77, P < 0.02 \) for Treatment × Time). Concentrations of serum glucagon (Fig. 1D) 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 \(-600 \mu V\) 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
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, $4.87 \pm 0.68$; human insulin, $5.93 \pm 0.54; P > 0.11$) and post-EEG recording values ($5.87 \pm 0.56$, $P > 0.91$) to low postingestion levels ($1.47 \pm 0.43$ vs. $1.00 \pm 0.24$, $P > 0.33; P > 0.12$ for

**TABLE 2**

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

Average DC-potential levels (in $\mu$V) 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 $\mu$V). 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 ± SE) | Detemir (mean ± SE) | P value |
|----------------------|---------------------------|---------------------|---------|
| Total intake (kcal)  | 1,559.79 ± 138.72         | 1,257.68 ± 82.41    | 0.04    |
| Carbohydrate (kcal)  | 803.18 ± 50.59            | 630.14 ± 49.76      | 0.06    |
| Fat (kcal)           | 554.53 ± 83.70            | 472.32 ± 61.31      | 0.20    |
| Protein (kcal)       | 202.09 ± 20.40            | 154.32 ± 13.41      | 0.004   |
| Carbohydrate (% of total intake) | 53.99 ± 3.20 | 53.99 ± 3.37 | 0.40 |
| Fat (% of total intake) | 33.19 ± 2.91      | 36.25 ± 3.24       | 0.32    |
| Protein (% of total intake) | 12.82 ± 0.49    | 12.36 ± 0.70       | 0.53    |
| Total intake (including glucose infusion; kcal) | 1,782.81 ± 133.73 | 1,475.34 ± 79.49 | 0.04 |
| Carbohydrate (including glucose infusion; kcal) | 1,026.20 ± 54.28 | 848.69 ± 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 × 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 vs. 2.20, P = 0.18) and reported increased wakefulness (sleepy-awake, 3.33 ± 0.23 vs. 2.73 ± 0.23, P < 0.03) and hunger (full-hungry, 4.20 ± 0.20 vs. 3.53 ± 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 increased 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.

ACKNOWLEDGMENTS

Supported by Deutsche Forschungsgemeinschaft (KFO 126/BS) and Novo Nordisk. The funding source had no input in the design and conduct of this study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the article.

M.H. and B.S. have received honoraria for speaking engagements by Novo Nordisk. W.K. has received grant support, honoraria for speaking engagements, and consulting fees for participating on scientific boards of Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

We thank Katrin Dieckmann and Nina Eggers for their expert assistance and Ingrid von Lützau, Martina Grohs, and Heidi Ruf for their invaluable laboratory work.

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