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DIABETES RESEARCH

COMPARATIVE STUDY OF HORMONAL COUNTER-REGULATION DURING GCIIS-GUIDED INSULIN HYPOGLYCEMIA TESTS USING HUMAN INSULIN (RECOMBINANT DNA) AND PORK INSULIN

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(Received 27 August 1984)

SUMMARY Human insulin (BHI, recombinant DNA) and pork insulin (PI) were compared in 10 healthy volunteers. Using a glucose controlled insulin infusion system for the performance of the insulin hypoglycemia test (IHT), a comparable dosage of both insulins had to be infused (BHI 0·129 ± 0·007 vs PI 0·115 ± 0·01 U/kg; mean ± SEM). Blood glucose slopes and nadirs did not differ significantly (BHI 30 ± 2 vs PI 29 ± 2 mg/dl). There was no difference in C-peptide inhibition (minimum for BHI 0·50 ± 0·08 vs PI 0·42 ± 0·08 µg/l). Maximum hormone responses were identical for ACTH (BHI 78·4 ± 11·3 vs PI 76·0 ± 8·7 pg/ml), cortisol (BHI 246 ± 20 vs PI 252 ± 15 ng/ml) and GH (BHI 43·8 ± 7·3 vs PI 49·4 ± 6·7 ng/ml). Peak levels of prolactin did not differ significantly (BHI 1,335 ± 315 vs PI 1,766 ± 614 µU/ml).

The urinary excretion pattern of epinephrine in three 120 min periods before, during and after IHT was identical (before IHT: BHI 0·9 ± 0·2 vs PI 0·6 ± 0·1 µg/120 min; during IHT: BHI 12·6 ± 2·2 vs PI 13·4 ± 2·5 µg/120 min; after IHT: BHI 2·5 ± 0·7 vs PI 3·7 ± 1·3 µg/120 min). No differences in the minima of serum potassium levels were observed (BHI 3·38 ± 0·04 vs PI 3·33 ± 0·05 mmol/l).

We conclude that the biological effects of human insulin and pork insulin are comparable. Our data do not support the assumption of a different hypothalamic handling of human insulin (recombinant DNA) and porcine insulin.

Key words: Human insulin (recombinant DNA), insulin hypoglycemia test, glucose controlled insulin infusion system

INTRODUCTION

STUDIES comparing the effect of human insulin (recombinant DNA) and pork insulin on hormonal counter-regulation after insulin-induced hypoglycemia have yielded contradictory results up to now (1–6). Concerning the counter-regulatory response of cortisol and growth hormone, a diminished as well as an increased secretion was reported (4, 7). Moreover, both decreased and increased inhibition of endogenous insulin secretion was observed (4, 5). Furthermore, Rosak and co-workers (5) found a blunted or deficient prolactin response under human insulin, whereas Petersen *et al.* (3) noticed that injection of human insulin resulted in less pronounced hypokalemia and epinephrine secretion. On the other hand, Landgraf (2) was not able to show any significant differences in counter-regulatory hormone responses.

Among these conflicting data, the differences in serum potassium, prolactin and epinephrine secretion, which may reflect a different hypothalamic handling of the insulins, are perhaps of clinical importance. However, as a result of very different insulin doses used in these studies, the comparability is limited. We therefore used a glucose controlled insulin infusion system (GCIIS) in order to perform the insulin hypoglycemia test (IHT) on the basis of a standardized hypoglycemia (8).

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Materials and Methods

Ten healthy volunteers (4 female, 6 male; 25±0·9 yr; 174±4 cm; 66±4 kg; (mean±SEM)) were studied after informed consent. Each subject underwent 2 insulin hypoglycemia tests: one with human insulin of recombinant DNA origin (Biohumaninsulin normal, ELI LILLY GMBH) and one with pork insulin (Insulin S, HOECHST).

Glucose Controlled Insulin Infusion System

The details of the GCIIS used for our study (Biostator, LIFE SCIENCE INSTRUMENTS, MILES LABORATORIES) have been described elsewhere (9–11). The Biostator was used on static control. The following constants were chosen: BI 35, QI 10, RI 20, FI 300.

Experimental Protocol

After an overnight fast and bed rest, the subjects were connected to the GCIIS between 8 am and 9 am. Feedback controlled insulin infusion was discontinued and the device was only used for blood glucose monitoring when blood glucose had fallen below 40 mg/dl and initial clinical symptoms of hypoglycemia like palpitations, headache, sweating, tachycardia and drowsiness occurred (8). Venous blood samples were drawn at −10, ±0, +10, +20, +30, +40, +60, +90 and +120 min, respectively, from an indwelling catheter placed in an antecubital vein. In addition, urine was collected during three 120 min periods before, during and after IHT.

Analytical Methods

Serum GH (CIS), prolactin (CIS), cortisol (clinical assays, SP), ACTH (INC, without extraction), insulin (CIS) and C-peptide (BYK Mallinckrodt) were measured by radioimmunoassay. Serum potassium was determined by flame photometry. Urinary epinephrine was measured by HPLC with electrochemical detection (12).

Statistical Methods

Results are expressed as mean±SEM. Wilcoxon's t-test for paired differences and analyses of variance (repeated measures over time) were used (13).

Results

Figures 1–4 and Table 1 show the results obtained with biosynthetic human insulin (BHI) and pork insulin (PI). The curves were obtained by calculating the mean values ± SEM at identical timepoints, whereas Table 1 gives the results obtained by calculating the mean±SEM of the individual peak or nadir levels, which differed slightly in time from the overall means.

A total of 0·129±0·007 U/kg BHI and 0·115±0·01 U/kg PI was given by the GCIIS (no statistically significant difference). Blood glucose values did not differ significantly for both insulins during IHT (fig. 1). The lowest blood glucose concentration was 30±2 for BHI and 29±2 for PI (not significant).

Peak values for serum insulin did not differ significantly (214±34 for BHI vs 172±14 mU/l for PI), whereas serum insulin levels at 20 min were higher for BHI than for PI (151±16 vs 214±34 mU/l; $p < 0·05$).

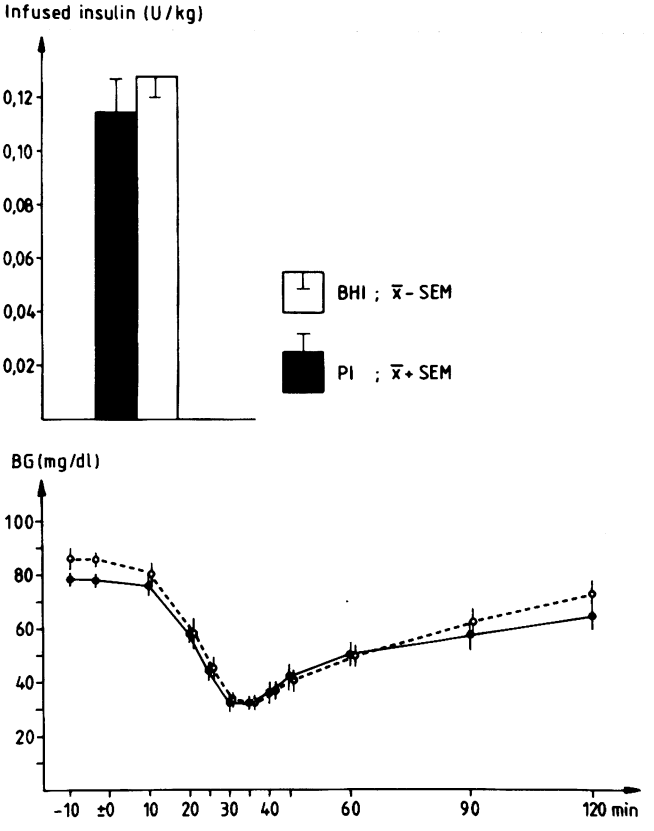

FIG. 1. Infused insulin and blood glucose levels during GCIIS-guided IHT with BHI O---O and PI ●——● in 10 healthy volunteers (mean±SEM).

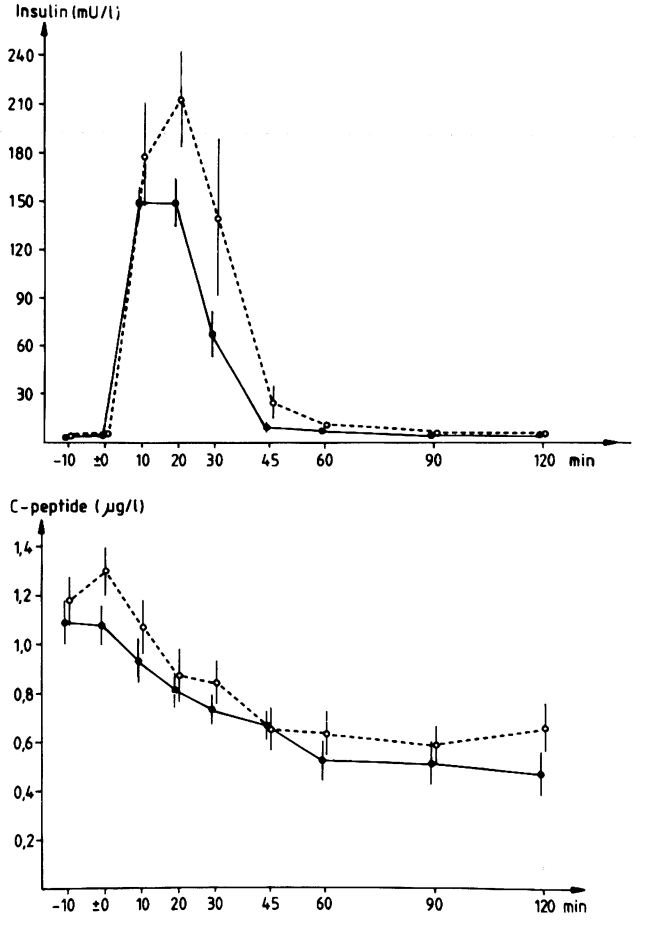

FIG. 2. Serum insulin and serum C-peptide concentrations during GCIIS-guided IHT with BHI O---O and PI ●——● in 10 healthy volunteers (mean±SEM).

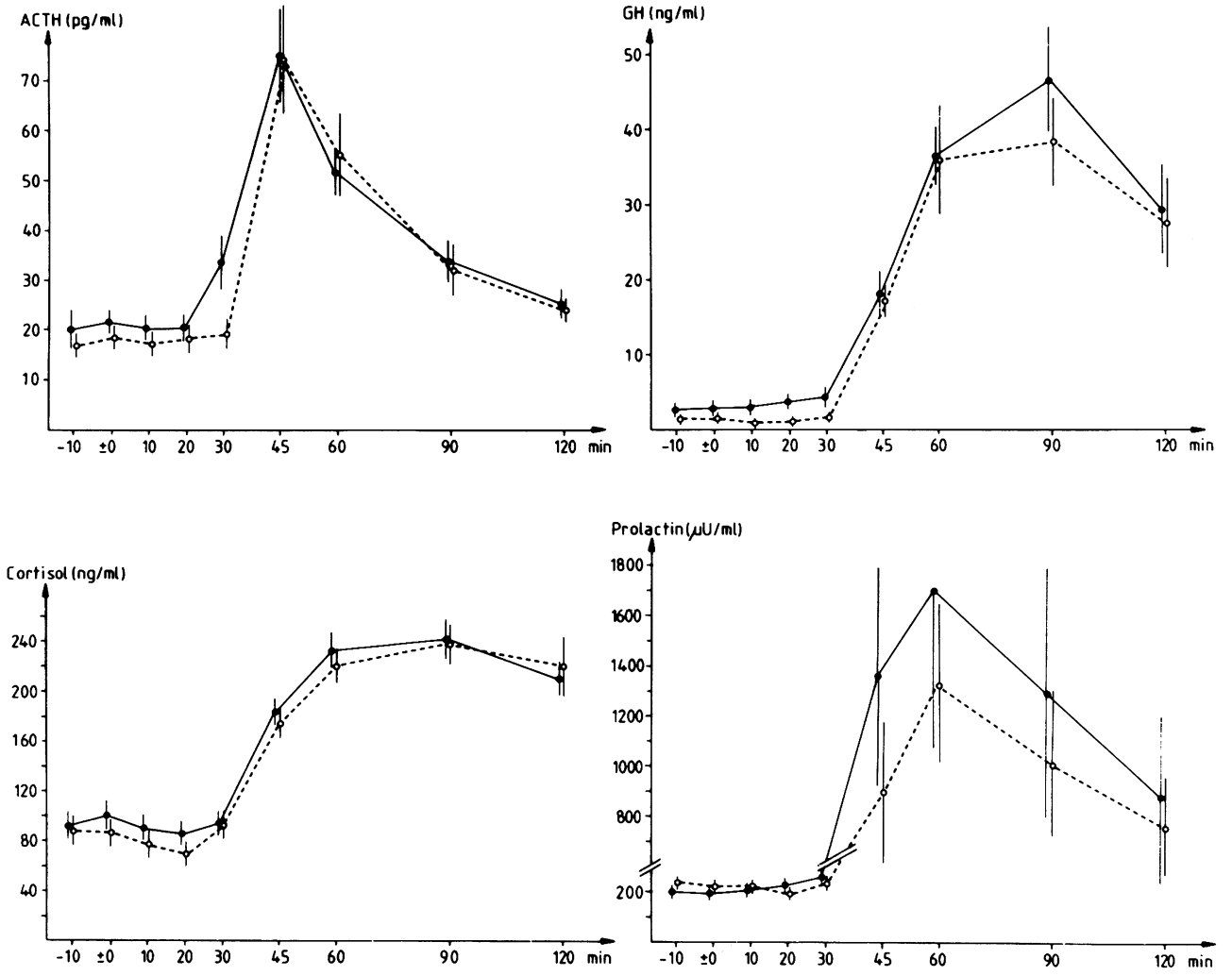

FIG. 3. Serum levels for ACTH, cortisol, GH and prolactin during GCIIS-guided IHT with BHI O---O and PI ●——● in 10 healthy volunteers (mean ± SEM).

Following BHI and PI administration, an identical pattern of C-peptide inhibition could be demonstrated (fig. 2). ACTH and cortisol responses were indentical for BHI and PI (fig. 3). ACTH reached its maximum at 45 min with 78·4 ± 11·3 pg/ml for BHI vs 76·0 ± 8·7 pg/ml for PI. Peak values for cortisol, observed at 90 min, were 246 ± 20 ng/ml for BHI and 252 ± 15 ng/ml for PI, respectively.

Identical slopes were obtained for GH. The maximal hormone response values were 43·8 ± 7·3 ng/ml for BHI and 49·4 ± 6·7 ng/ml for PI; the difference was statistically not significant. The same was true with prolactin secretion. After administration of both insulins, prolactin reached its maximum after 60 min: 1,335 ± 315 µU/ml (BHI) and 1,766 ± 614 µU/ml (PI). Although prolactin levels following BHI administration tended to be lower than after PI, a statistically significant difference could not be detected (fig. 3).

Following insulin administration, the decline of serum potassium was virtually identical (fig. 4). The minimal values were 3·38 ± 0·04 mmol/l (BHI) and 3·33 ± 0·05 mmol/l (PI).

The urinary excretion pattern of epinephrine, as evaluated by its content in three 120 min periods before, during and after IHT, did not differ significantly: during IHT 12·6 ± 2·2 µg for BHI vs 13·4 ± 2·5 µg for PI; after IHT 2·5 ± 0·7 µg for BHI vs 3·7 ± 1·3 for PI.

Discussion

The aim of this investigation was to study the counter-regulatory effects following BHI and PI administration during standardized hypoglycemia achieved by automatic adjustment of insulin delivery to the individual insulin sensitivity by means of the GCIIS (8). As shown, nearly identical amounts of infused insulin produced comparable serum insulin peaks and resulted in identical blood glucose responses. So we feel that—in spite of some minor differences in serum insulin levels, which may be in part attributed to the different insulin formulations (14)—the results obtained with BHI and PI are comparable.

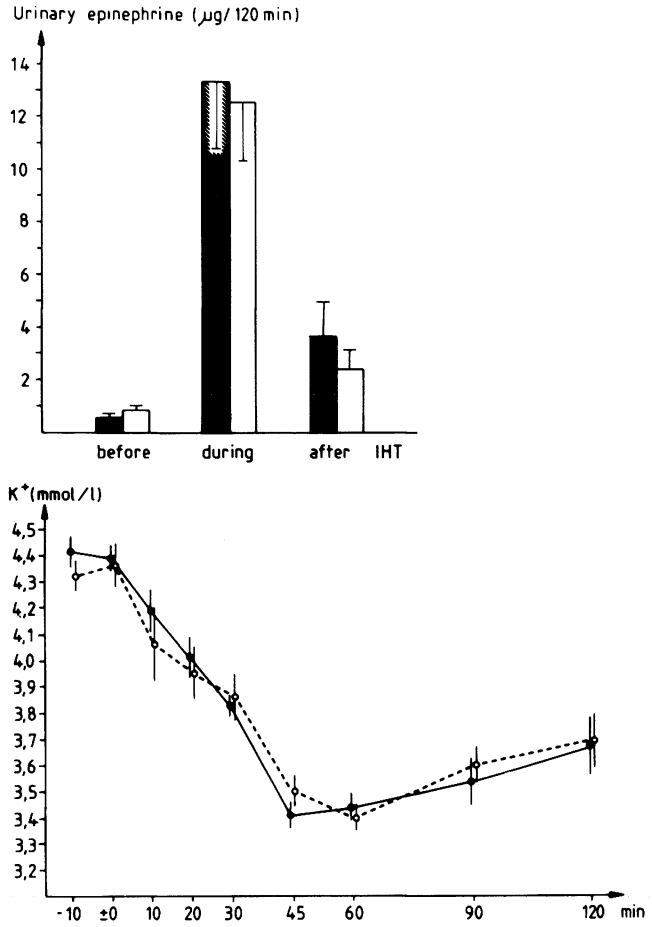

FIG. 4. Urinary epinephrine before, during and after GCIIS-guided IHT with BHI □ and PI ▨ in 10 healthy volunteers (mean ± SEM). Serum potassium concentrations for BHI ○---○ and PI ●——● are also shown (mean ± SEM).

The inhibition pattern of endogenous insulin secretion during IHT as reflected by serum C-peptide levels showed no differences after BHI and PI.

No differences in glucose counter-regulation with regard to the hypothalamic-pituitary-adrenocortical axis could be detected.

Furthermore, we were not able to see a deficient prolactin response during IHT as reported by others (5). The failure to detect any statistically significant difference in prolactin secretion does not necessarily imply that the hormonal responses for both insulins are identical, because of the large standard deviation in a limited number of subjects. However, it is doubtful, whether a blunted response, which has recently been shown only after a dosage of 0·075 U/kg insulin (2, 5), has any clinical importance.

With the assumption that the epinephrine secretion is reflected with sufficient reliability by the urinary epinephrine excretion during the collection periods, no differences in counter-regulatory epinephrine responses could be demonstrated. A distinct decrease of serum potassium concentrations occurs during insulin-induced hypoglycemia. The initial decline is due to the insulin-induced cell-influx, whereas the second phase after blood glucose recovery is attributed to epinephrine secretion in response to hypoglycemia (5, 15, 16). According to the identical epinephrine excretion pattern, we could not find any differences in serum potassium concentrations during IHT. These findings confirm recent data (2), but are in contrast to Petersen and co-workers (3) who described less pronounced changes in serum potassium and epinephrine after injection of 0·1 U/kg BHI when compared to an identical pork insulin formulation.

Table 1 Mean basal values (bas.) and maximum (max.) or minimum (min.) levels obtained during GCIIS-guided IHT with BHI and PI for blood glucose (BG), C-peptide, prolactin, ACTH, cortisol, GH, serum potassium and urinary epinephrine in 10 healthy volunteers (mean ± SEM)

	BG (mg/dl)		*C-peptide (µg/l)*		*Prolactin (µU/ml)*	
	bas.	*min.*	*bas.*	*min.*	*bas.*	*max.*
BHI	85 ± 3	30 ± 2	1·25 ± 0·10	0·50 ± 0·08	214 ± 24	1,335 ± 315
PI	79 ± 3	29 ± 2	1·08 ± 0·08	0·42 ± 0·08	207 ± 25	1,766 ± 614
	ACTH (pg/ml)		*Cortisol (ng/ml)*		*GH (ng/ml)*	
	bas.	*max.*	*bas.*	*max.*	*bas.*	*max.*
BHI	16·7 ± 2·2	78·4 ± 11·3	85 ± 11	246 ± 20	1·3 ± 0·4	43·8 ± 7·3
PI	18·5 ± 2·6	76·0 ± 8·7	94 ± 9	252 ± 15	2·3 ± 1·0	49·4 ± 6·7
	Potassium (mmol/l)		*Urinary epinephrine (µg/120 min)*			
	bas.	*min.*	*before*	*during*	*after IHT*	
BHI	4·29 ± 0·09	3·38 ± 0·04	0·9 ± 0·2	12·6 ± 2·2	2·5 ± 0·7	
PI	4·30 ± 0·04	3·33 ± 0·05	0·6 ± 0·1	13·4 ± 2·5	3·7 ± 1·3	

We conclude that the biological effects of human insulin (recombinant DNA) and pork insulin are comparable. Our data do not support the assumption of a different hypothalamic handling of human and porcine insulin (3, 6) which might have been of clinical importance in diabetes treatment.

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