Less Pronounced Changes in Serum Potassium and Epinephrine During Hypoglycemia Induced by Human Insulin (recombinant DNA)

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Human insulin (recombinant DNA) and purified porcine insulin were compared in healthy men. Intravenous insulin tolerance tests showed identical effects on plasma glucose when a bolus of 0.1 U/kg was injected. Following human insulin, hypokalemia and epinephrine secretion were significantly less pronounced. The differences in serum potassium concentrations are caused by a lower epinephrine response to hypoglycemia induced by human insulin in comparison to purified porcine insulin. DIABETES CARE 5 (SUPPL. 2): 90–92, 1982.

A dissociation of plasma glucose and serum potassium in response to intravenous insulin occurs at plasma glucose concentrations below 30 mg/dl. The effect of an intravenous bolus of insulin on plasma glucose is shorter than the effect on serum potassium.[1] Following an intravenous bolus of insulin, the nadir of glucose is reached after 20 min, while serum potassium continues to decline for a further 25 min.[1]

A short-term redistribution of whole-body potassium can be induced by insulin[2] and by epinephrine.[3] These hormones stimulate cellular K^+-Na^+ ATPase by different mechanisms.[4–6] As a result, cellular potassium uptake is increased and the serum potassium concentration declines. The effect of epinephrine can be inhibited by beta-adrenoceptor blockade.[7] Experiments with propranolol[8] revealed that the decrease of serum potassium during severe insulin-induced hypoglycemia is the result of the combined effects of insulin and epinephrine. Epinephrine secretion occurs in response to low plasma glucose concentrations resulting in a prolonged decline of serum potassium while glucose normalizes.[8] We have compared the effects of human insulin (recombinant DNA) to identically formulated native porcine insulin in healthy male volunteers.

METHODS

Human insulin and purified porcine insulin in identical formulation were obtained from Eli Lilly and Company, Indianapolis, Indiana. Intravenous insulin tolerance tests (bolus of 0.1 U/kg body wt) were performed in six healthy volunteers (age 24.1 ± 2.2 yr, body weight 74.8 ± 7.3 kg, height 183.2 ± 6.6 cm) after an overnight fast in a randomized, double-blind study. Informed consent was obtained. Physical examination, ECG, laboratory chemistry and oral glucose load were normal. Venous blood samples were drawn at the times indicated.

Plasma glucose was analyzed with the Beckman Glucose Analyzer (GOD method). Serum insulin was measured by RIA (Phadebas Insulin Test, Pharmacia Diagnostics, Uppsala, Sweden). Serum potassium was assessed by flame photometry. Plasma catecholamines were collected and determined.[9]

Results are expressed as mean ± SEM. Interassay variations were below 5% using individual assays for each volunteer. Areas under the curves were calculated according to the equation

$$\sum_{n=1}^{n-1} \frac{(x_{n+1} - x_n)\,(y_{n+1} + y_n)}{2}.$$

Wilcoxon's *t*-test for paired differences was used.

RESULTS

The effect on plasma glucose concentrations of an intravenous bolus of identically formulated human or naturally occurring porcine insulin is shown in Figure 1. Identical slopes and nadirs were observed after a bolus of 0.1 U/kg body wt in healthy volunteers. Minimal glucose concentrations were observed after 20 min.

Serum potassium concentrations (Figure 2) decline in response to the intravenous bolus of insulin for 45 min. At

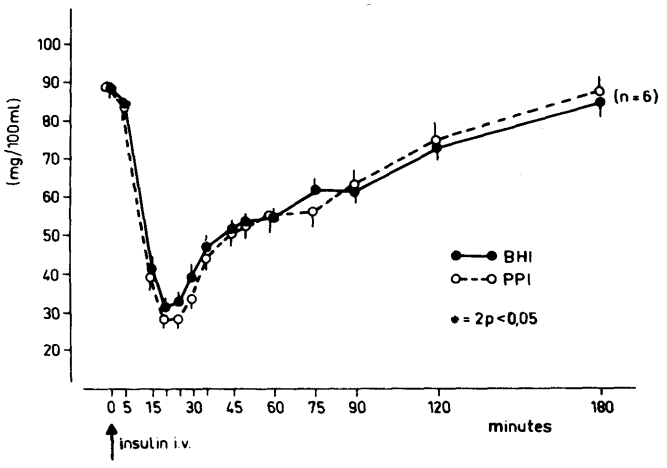

FIG. 1. Plasma glucose concentrations after an intravenous bolus of 0.1 U/kg body wt of human insulin (BHI) or purified porcine insulin (PPI) in healthy volunteers. Mean ± SEM.

the glucose nadir after 20 min the mean serum potassium concentration is lowered by 0.5 mmol/L following both human and naturally occurring porcine insulin. While glucose normalizes there is an additional decrease of serum potassium concentration.

The decrease of serum potassium during min 20–45 is more pronounced after purified porcine than after human insulin. The areas below the time concentration curves (0–180 min) are significantly different (human insulin: 114.8 ± 17.3; purified porcine insulin: 60.9 ± 12.5), ($2P < 0.05$).

Figure 3 shows the secretion patterns of epinephrine, norepinephrine, and dopamine during insulin-induced hypoglycemia. Elevations of plasma dopamine were not observed. Slight elevations of norepinephrine occurred in response to both insulins. A significant increase of epinephrine secretion

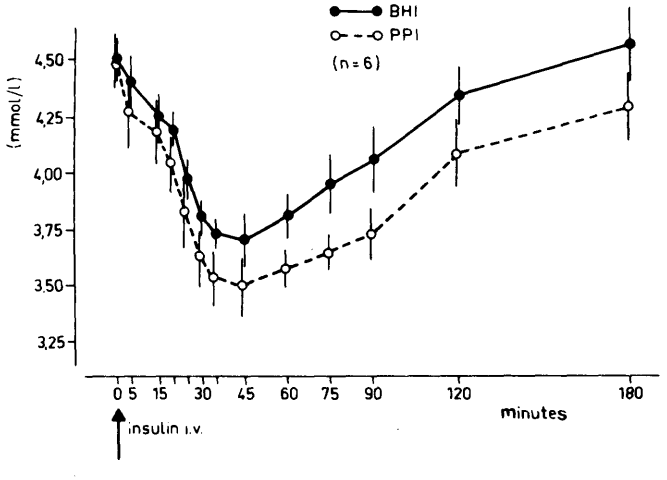

FIG. 2. Serum potassium concentrations after an intravenous bolus of 0.1 U/kg body wt human insulin (BHI) or purified porcine insulin (PPI) in healthy volunteers. Mean ± SEM.

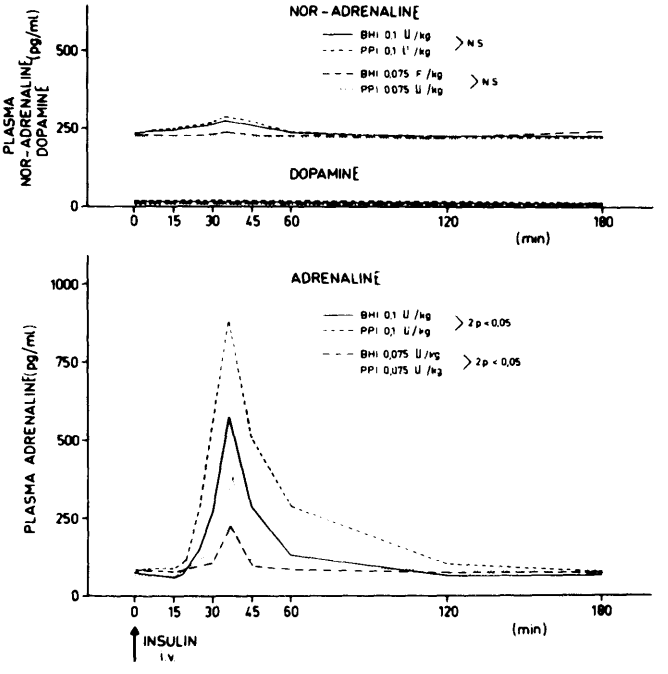

FIG. 3. Plasma epinephrine, plasma norepinephrine, and plasma dopamine after an intravenous bolus of 0.075 and 0.1 U/kg body wt in healthy volunteers.

was measured 20 min after the intravenous injection of insulin. The counterregulatory response of epinephrine was significantly more pronounced after purified porcine than after human insulin (areas below the curves: human insulin: 62,731 ± 26,954; purified porcine insulin: 74,372 ± 27,113) ($2P < 0.05$).

DISCUSSION

Intravenous insulin tolerance tests in healthy men produced identical nadirs of plasma glucose but a significantly lower response of epinephrine and a less pronounced decrease of serum potassium in response to human than to porcine insulin. During severe hypoglycemia serum potassium is initially lowered by insulin. At low glucose levels counterregulatory catecholamines produce opposite effects on plasma glucose and on serum potassium.[8]

Epinephrine induces a redistribution of whole body potassium by activating the cellular K^+-Na^+ ATPase.[4-6] The decrease of serum potassium during the late phase of hypoglycemia is the result of a stimulation of cellular potassium uptake.[9] The lower degree of hypokalemia is the consequence of a less pronounced secretion of epinephrine during hypoglycemia induced by human insulin.

In diabetic patients neuropathy intereferes during hypoglycemia. The adrenal medulla is not sensitive to glucose itself. Epinephrine secretion in response to hypoglycemia is mediated by the autonomic nervous system.[10] Abnormal basal and stimulated epinephrine secretion can result from auto-

nomic neuropathy in diabetic subjects.[11] It is difficult to predict the effects of human insulin in comparison to porcine insulin in diabetic patients. Newly diagnosed diabetic patients without neuropathy may be compared with the healthy men in this study, and human insulin treatment may be beneficial. The neural stimulus that promotes epinephrine secretion in response to low plasma glucose points to the central nervous system. The effects observed in this study may reflect a different handling of human and porcine insulin by the central nervous system.

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Dedicated to Prof. G. W. Löhr on the occasion of his 60th birthday.

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REFERENCES

[1] Schlüter, K. J., Petersen, K.-G., Borsche, A., Hobitz, H., and Kerp, L.: Effects of fully synthetic human insulin in comparison to porcine insulin in normal subjects. Horm. Metab. Res. *13*: 657–59, 1981.

[2] DeFronzo, R., Felig, P., Ferranini, E., and Wahren, J.: Effect of graded doses of insulin on splanchnic and peripheral potassium metabolism in man. Am. J. Physiol. *238*: 421–27, 1980.

[3] D'Silva, J. L.: The action of adrenaline on serum potassium. J. Physiol. *83*: 393–98, 1934.

[4] Clausen, T., and Flatman, J. A.: The effect of catecholamines on Na-K transport and membrane potential in rat soleus muscle. J. Physiol. *270*: 383–84, 1977.

[5] Gavryck, W. A., Moore, R. D., and Thomspon, R. C.: Effect of insulin upon membrane-bound (Na^+ + K^+)-ATPase extracted from frog skeletal muscle. J. Physiol. *252*: 43–58, 1975.

[6] Moore, R. D.: Stimulation of Na:H exchange by insulin. Biophys. J. *33*: 203–10, 1981.

[7] Castro-Tavares, J.: A comparison between the influence of pindolol and propranolol on the response of plasma potassium to catecholamines. Arzneimittel-Forsch. *26*: 238–41, 1976.

[8] Petersen, K.-G., Schlüter, K. J., and Kerp, L.: The regulation of serum potassium during insulin-induced hypoglycemia. Diabetes *31*: 615–17, 1982.

[9] Wehrli, A.: J. Chromatography, 1982. In press.

[10] Palmer, J. P., Henry, D. P., Benson, W. I., Johnson, D. G., and Ensick, I. W.: The glucagon response to hypoglycemia in sympathectomized man. J. Clin. Invest. *57*: 522–25, 1976.

[11] Hilsted, J., Gallo, H., and Christensen, N. J.: Impaired response of catecholamines, growth hormone, and cortisol to graded exercise in diabetic autonomic neuropathy. Diabetes *29*: 257–61, 1980.