Regulation of Serum Potassium During Insulin-induced Hypoglycemia

KARL-GEORG PETERSEN, KLAUS JOACHIM SCHLÜTER, AND LOTHAR KERP

SUMMARY

Counterregulatory secretion of epinephrine occurs during severe insulin-induced hypoglycemia. Under these conditions (minimal plasma glucose 27.4 ± 1 mg/dl) the decrease of serum potassium concentration (0.9 mVal/L) is mediated by two mechanisms: insulin-induced (0.48 mVal/L) and epinephrine-induced (0.42 mVal/L) cellular uptake of potassium. Epinephrine-induced serum potassium uptake appears to be more sensitive to beta-adrenoceptor blockade than glucose production. The intensification of insulin-induced hypokalemia by epinephrine is of clinical significance. DIABETES 31:615–617, July 1982.

During insulin-induced hypoglycemia there is a dose-dependent decrease of serum potassium concentration.[1] This is explained as an insulin-induced influx of K^+ ions into the cells. After a bolus injection of insulin (0.1 U/kg body wt) serum potassium continues to decrease while glucose normalizes.[2] This observation suggests different mechanisms during the early and late phase for the decrease of serum potassium during severe insulin-induced hypoglycemia. While moderate hypoglycemia is essentially compensated for by glucagon, severe hypoglycemia induces the additional secretion of epinephrine.

METHODS

Eight male volunteers without a family history of diabetes gave informed consent (age: 24.3 ± 1.0 yr, body weight: 71.9 ± 1.7 kg, height: 181.4 ± 2.4 cm). Physical examination, ECG, laboratory chemistry, and oral glucose load were normal.

Two insulin tolerance tests were performed in each volunteer with an oral dose of placebo or 160 mg propranolol in a randomized, double-blind study at intervals of 2 wk. An indwelling catheter was inserted into the right antecubital vein after an overnight fast (12 ± 1 h). Two hours after placebo or propranolol, an intravenous bolus (0.1 U/kg body wt) of pork insulin (Insulin-CS, Hoechst, Frankfurt) was injected. Venous blood samples were drawn at −10, 0, 5, 15, 25, 30, 35, 40, 45, 60, 75, 90, 120, 150, and 180 min.

Propranolol (160 mg) is frequently used in the treatment of hypertension. During hypoglycemia increases of heart rate (controls: 86.7 ± 3.9 beats/min; propranolol: 58.1 ± 5.6 beats/min) and of blood pressure amplitude (controls: 62.1 ± 4.2 mm Hg; propranolol: 30.0 ± 2.4 mm Hg) were prevented.

Plasma glucose was analyzed with the Beckman Glucose Analyzer (glucose-oxidase method) (Beckman Instruments, Fullerton, California). Serum insulin was estimated by RIA (Phadebas-Insulin-Test, Pharmacia Diagnostics, Uppsala, Sweden). Serum potassium was assessed by flame photometry. Plasma catecholamines were collected and determined according to DaPrada et al.[3]

Results are expressed as mean ± SEM. Interassay variations were below 5.0% 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

Two hours following an oral dose of placebo or of 160 mg propranolol, serum insulin, plasma glucose, serum potassium, plasma epinephrine, and plasma norepinephrine were recorded after an intravenous bolus of insulin (0.1 U/kg body wt) as shown in Figure 1.

The peak values of serum insulin were not influenced by beta-adrenoceptor blockade, but there was a delayed clearance of insulin 30–45 min after insulin injection ($2P < 0.01$).

From the Department of Medicine, Albert-Ludwigs-Universität Freiburg. Hugstetterstr. 55, D 7600 Freiburg, FRG.
Address reprint requests to Dr. Petersen at the above address.
Received for publication 2 November 1981 and in revised form 16 March 1982.

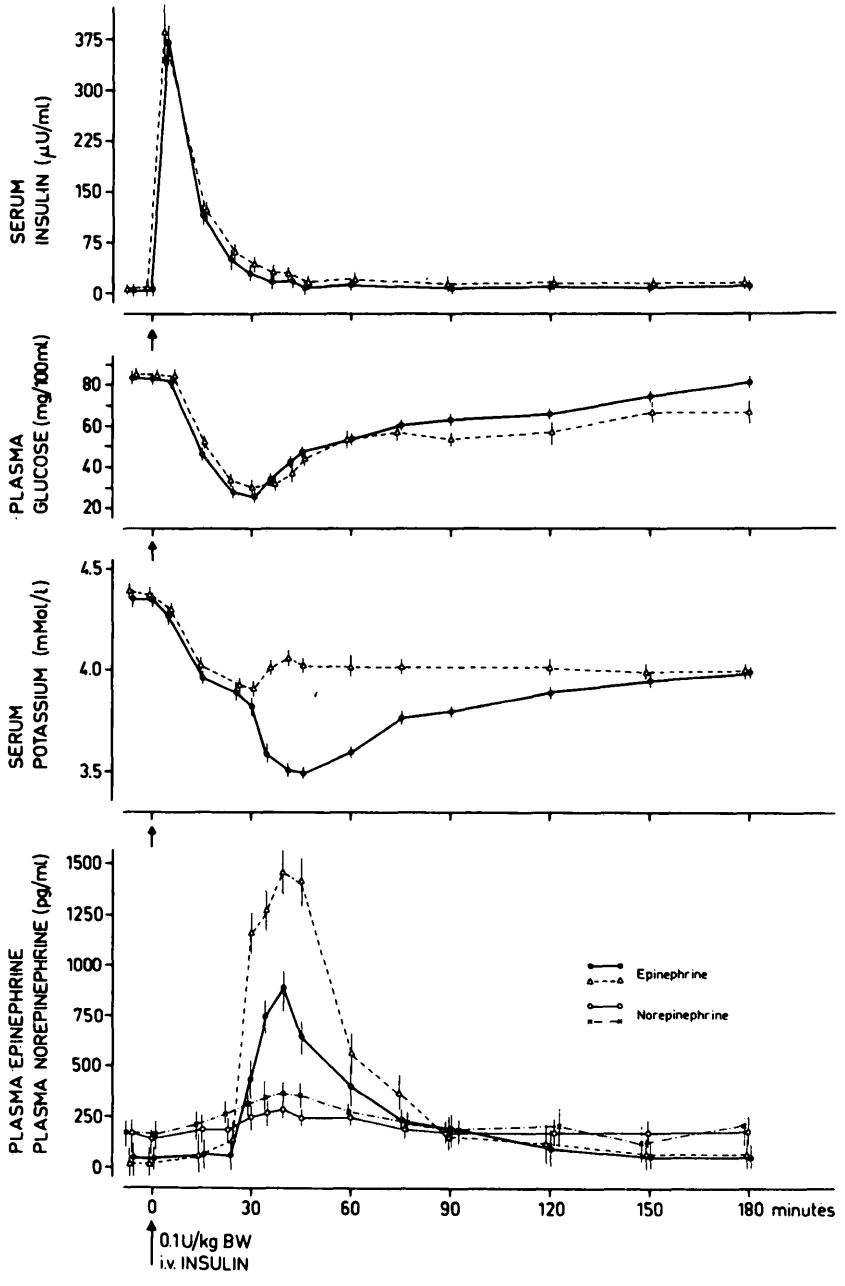

FIGURE 1. Effects of an oral dose of propranolol (160 mg) (—△— —△) and placebo (●——●) on serum insulin, plasma glucose, serum potassium, plasma epinephrine, and plasma norepinephrine during insulin-induced hypoglycemia (0.1 U/kg body wt) in volunteers (N = 8). The data are expressed as mean ± SEM.

Identical nadirs (27.4 ± 1.7 mg/dl) of plasma glucose were observed. The nadir following propranolol was significantly ($2P < 0.01$) delayed compared with placebo.

An immediate decrease of serum potassium was observed after the bolus injection of insulin following placebo or propranolol treatment. The concentration curves were identical for 25 min. In the placebo group serum potassium continued to decline for an additional 0.4 mmol/L at 45 min while propranolol administration prevented a further decline. Potassium levels in controls and after propranolol were significantly ($2P < 0.01$) different from minutes 35 to 120.

The counterregulatory output of epinephrine occurred at plasma glucose concentrations below 30 mg/dl 25–30 min after insulin injection. The peak concentrations were measured at 40 min. In the propranolol group epinephrine secretion was markedly enhanced (area: 121,729 ± 10,983 versus placebo 69,079 ± 8270, $2P < 0.05$). Norepinephrine did not increase in the placebo group, but there was a significant output following propranolol treatment ($2P < 0.05$).

DISCUSSION

The immediate decline of serum potassium concentration in response to an i.v. bolus of insulin is not modified by beta-adrenoceptor blockade. An involvement of beta-adrenoceptors in the initial potassium uptake is thus improbable. The decline of serum potassium concentration, which begins at the nadir of glucose and coincides with the output of epinephrine, can be blocked by propranolol. The decline of serum potassium from 30 min to the nadir at 45 min in the placebo group appears to be caused by beta-adrenoceptor stimulation due to elevated epinephrine concentrations.

This is in accordance with previous reports that epinephrine infusion causes hypokalemia.[4,5]

Studies with isolated rat soleus muscle in glucose-free bicarbonate buffer indicated that catecholamines induce a new steady-state distribution of Na and K by activating the $(Na^+ + K^+)$-ATPase.[6] The effect of epinephrine was suppressed by propranolol.[6] Insulin also stimulates the activity of membrane-bound ATPase.[7] Experiments in frog skeletal muscle[8] show that insulin induces an increase in sodium permeability and intracellular pH. As a consequence, $(Na^+ + K^+)$-ATPase is activated, sodium is ejected from the cell, and potassium flows in, resulting in hypokalemia.[8]

Our results are in accordance with the assumptions based on in vitro studies. Insulin and epinephrine stimulate cellular potassium uptake by independent mechanisms. The insulin-induced activation is not inhibited by propranolol.

The seriously augmented secretion of epinephrine in the volunteers treated with propranolol is sufficient to produce a recovery from hypoglycemia comparable to controls. The increased amount of plasma epinephrine is obviously not able to overcome the inhibition of serum potassium uptake caused by beta-adrenoceptor blockade.[9,10] This result suggests differences in the mechanisms mediating glucose production[11] and potassium uptake[1] by epinephrine in man.

As discussed, hypokalemia subsequent to insulin is intensified if a stimulation of epinephrine in addition to glucagon[11] occurs at low plasma glucose concentrations. Hypoglycemia is one of several reasons for an increase of plasma epinephrine concentration. Clinical situations imply more elevated and sustained levels of both insulin and epinephrine. The contribution to hypokalemia can be more pronounced. It is clinically significant to avoid epinephrine stimulation during intensive insulin treatment.

ACKNOWLEDGMENT

This work was supported by the Sandoz-Stiftung für therapeutische Forschung.

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