Effects of Adrenergic Blockade on Serum Potassium Changes in Response to Acute Insulin-Induced Hypoglycemia in Nondiabetic Humans

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Objective: To determine the possible role of adrenergic mechanisms in mediating the fall in serum potassium concentration after intravenous injection of insulin. Research Design and Methods: Eighteen nondiabetic male volunteers, divided into three groups of six subjects, comprised the study. Hypoglycemia was induced by a bolus of short-acting insulin (0.15 U/kg body wt). Six subjects were studied in control conditions, six during α-adrenergic blockade with phentolamine, and six during β-adrenergic blockade with propranolol. Results: In the control group, there was an immediate fall in serum potassium from 4.0 ± 0.1 to 3.6 ± 0.1 mM at baseline + 15 min. After the onset of acute hypoglycemia, potassium decreased further in the control group, reaching a lowest concentration of 3.3 ± 0.1 mM. In the propranolol group, the late decrease in potassium was inhibited, and there were no further changes in serum potassium. During α-blockade, there was an exaggerated fall to 2.6 ± 0.1 mM at 30 min after the onset of hypoglycemia. Conclusions: The later fall in serum potassium, which occurs after the onset of hypoglycemia, is probably mediated by stimulation of β-adrenoreceptors, whereas coincidental stimulation of α-adrenoreceptors opposes this fall in potassium and may prevent the development of severe hypokalemia in response to acute hypoglycemia. *Diabetes Care* 14:548–52, 1991

In humans, the intravenous injection of soluble insulin causes a biphasic fall in serum potassium concentration (1). The immediate reduction in potassium within 15 min of the injection of insulin is probably the result of direct stimulation by insulin of potassium influx into cells (1). A later and more profound fall in serum potassium occurs after the development of acute hypoglycemia (2,3), which coincides temporally with secretion of epinephrine from the adrenal medulla. The intravenous infusion of epinephrine causes a reduction in serum potassium, and the decline in potassium during epinephrine infusion and hypoglycemia can be inhibited by β-adrenergic blockade (3–5), suggesting that the fall in serum potassium after hypoglycemia may be caused by the stimulation of β-adrenoreceptors by circulating epinephrine (3). In this study, the responses of serum potassium, epinephrine, and norepinephrine were examined in nondiabetic human subjects after the injection of soluble insulin and during the subsequent development of acute hypoglycemia in control conditions, during α- and β-adrenergic blockade, to elucidate the putative adrenergic mechanisms involved in mediating these responses.

RESEARCH DESIGN AND METHODS

Approval for the study was given by the local medical ethical advisory committee, which stated that the performance of repeated studies in individual subjects was not acceptable; therefore, each subject was made hypoglycemic on one occasion only. Informed consent was obtained from all subjects. Eighteen nondiabetic healthy male subjects, none of whom were taking any medication, aged 21–30 yr, were studied in a random order. Six subjects were studied under control conditions (control group). Six subjects were studied during nonselec-

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tive α-adrenergic blockade with phentolamine and received 5 mg i.v. injected as a bolus followed by an intravenous infusion of 30 mg/h (6–8). Six subjects were studied during nonselective β-adrenergic blockade with propranolol and received 10 mg i.v. injected as a bolus followed by an intravenous infusion of 3 mg/h (9–11). All subjects had a normal body mass index, and there was no significant difference in the mean body mass index for the groups, which was 22 ± 2 kg/m^2 for the control group, 21 ± 2 kg/m^2 for the group treated with phentolamine, and 23 ± 2 kg/m^2 for the group treated with propranolol.

Subjects were studied after an overnight fast in a recumbent posture throughout the study. Exercise was prohibited on the morning of the study. At 0800, an indwelling Teflon cannula was inserted into an antecubital vein. Pharmacological blockade with either phentolamine or propranolol commenced at 0830. At 0900, basal blood samples were taken, and soluble insulin (Human Actrapid, Novo, Basingstoke, Hants, UK) was administered as an intravenous bolus injection in a dose of 0.15 U/kg body wt. Serial sampling of blood for the estimation of blood glucose with a Reflolux II glucometer (BCL, Lewes, UK) and measurements of heart rate and blood pressure were made at intervals of 5 min to determine the onset of the acute autonomic reaction (R). This onset (R) coincided with the lowest concentration of blood glucose in all subjects. A wide variation is found in the time to reach the blood glucose nadir in nondiabetic subjects, with a range of 20–45 min (11). To accommodate this individual variation in the time from the administration of insulin to the onset of the acute autonomic reaction, subsequent blood sampling was timed from R to eliminate the individual variability in the time taken to develop hypoglycemia after the injection of insulin, as done in previous studies (2,9–11). Blood sampling was continued until R + 90 min. Blood glucose was measured at 15-min intervals and serum potassium at 15-min intervals until R + 30 min, when sampling was reduced to 30-min intervals, and catecholamines were sampled at baseline, R, R + 15 min, R + 30 min, and R + 60 min.

Serial measurements of blood pressure were made with a mercury sphygmomanometer. The heart rate was measured continuously with precordial electrodes with the heart rate displayed on an oscilloscope (Life Trace 12, Albrae, London). Blood glucose was measured with the Cobas biocentrifugal analyzer (Roche, Basel, Switzerland) with a hexokinase method. Serum potassium was measured by flame photometry, and plasma epinephrine and norepinephrine were measured by radioenzymatic assays (12).

Statistical analyses were performed with the Statview 512 package (Brainpower, Calabasas, CA) on an Apple Macintosh SE Computer (Cupertino, CA). Serial comparisons for blood glucose and catecholamines were made with analysis of variance (ANOVA) for repeated measures and with post hoc comparisons with Student's *t* test for unpaired data. For analysis purposes, the changes in serum potassium were divided into two time periods. The initial change in serum potassium between basal sampling and basal +15 min was compared with ANOVA. The later changes in serum potassium were compared to the concentration at 0 + 15 min with Student's *t* test for paired data and to the control group with ANOVA for repeated measures.

RESULTS

All subjects developed objective evidence of hypoglycemia with sweating and moderate neuroglycopenia. The hemodynamic responses associated with hypoglycemia were observed in the control group, comprising an increase in heart rate, a rise in systolic blood pressure, and a fall in diastolic pressure with no change in the mean arterial pressure (10). During α-adrenergic blockade, subjects developed nasal congestion, tachycardia, and flushing of the extremities. After hypoglycemia, a further significant increase in heart rate was observed, and a significant reduction in the systolic, diastolic, and mean arterial blood pressure occurred in all subjects. During β-blockade, the subjects experienced no symptoms, and the heart rate did not increase in response to hypoglycemia. Significant increases were observed in the systolic, mean, and diastolic blood pressures, which have been described previously during hypoglycemia with β-blockade (10). No difference in the time of onset of R after insulin administration was observed between the three studies, and the time of R was basal + 28 ± 2 min in the control group, basal + 26 ± 2 min in the phentolamine group, and basal + 27 ± 2 min in the propranolol group.

In the control group, the mean blood glucose level fell significantly from 4.6 ± 0.1 mM at baseline to a lowest concentration of 1.0 ± 0.2 mM at the onset of the acute autonomic reaction R. No significant differences in mean basal blood glucose or the pattern of blood glucose recovery were observed during α-adrenergic blockade with phentolamine compared with the control group (Fig. 1). In the group treated with propranolol, the blood glucose level was similar to the control group at 1.0 ± 0.1 mM at R. Thereafter, blood glucose recovery was slower than the control group (ANOVA, $P < 0.01$) and was significantly lower at all times of measurement (*t* test, $P < 0.05$ compared to control group at all times).

In the control group, the serum potassium decreased from a basal concentration of 4.0 ± 0.1 to 3.6 ± 0.1 mM after the injection of insulin at basal + 15 min (*t* test, $P < 0.05$ compared to basal). In the group treated with phentolamine, the early fall in serum potassium to 3.4 ± 0.1 mM at basal + 15 min was not significantly different from the control group (ANOVA, $P = 0.34$). Similarly, during β-blockade with propranolol, the initial fall in potassium to 3.5 ± 0.1 mM at basal + 15 min was not significantly different from the control group (ANOVA, $P = 0.19$).

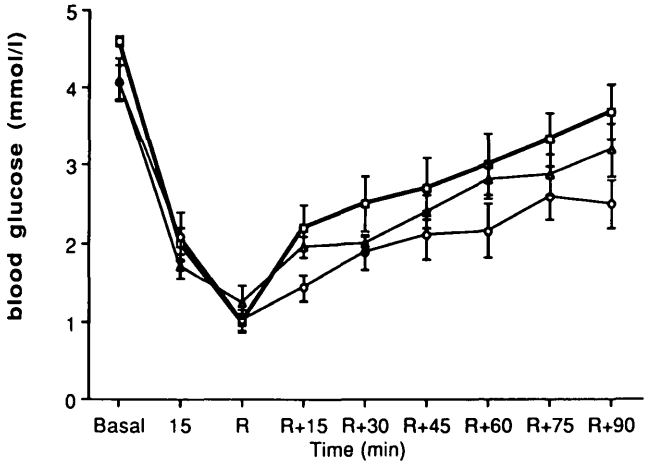

FIG. 1. Changes in blood glucose in response to insulin-induced hypoglycemia in control study (□), during α-adrenergic blockade with phentolamine (△), and during β-adrenergic blockade with propranolol (○). Insulin was given immediately after basal sampling. R, acute autonomic reaction. Values are means ± SE.

In the control group, the serum potassium level continued to fall as hypoglycemia developed, reaching a lowest concentration of 3.2 ± 0.1 mM at R + 15 min (*t* test, $P < 0.001$ compared to control basal + 15 min). In the group treated with phentolamine, a greater fall in serum potassium was observed, reaching a lowest concentration of 2.6 ± 0.1 mM at R + 30 min (ANOVA, $P < 0.05$ compared to the control group for basal + 15 min to R + 90 min). In the group treated with propranolol, no further decrease in serum potassium was observed after the onset of hypoglycemia, but this was not significantly different from the responses in the control group (ANOVA, $P = 0.1$; Fig. 2).

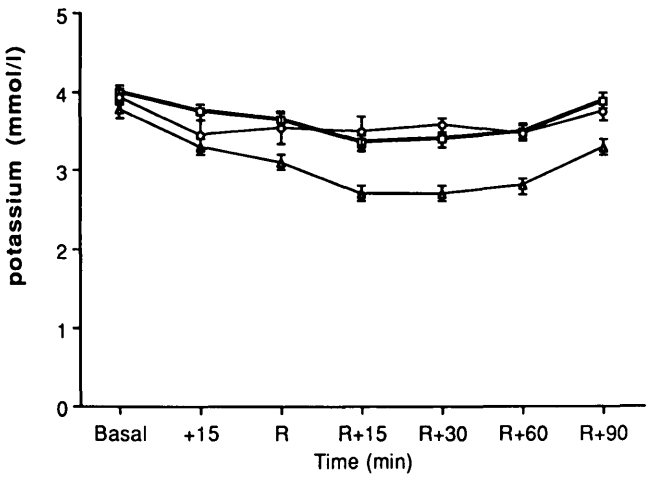

FIG. 2. Changes in serum potassium in response to insulin-induced hypoglycemia in control study (□), during α-adrenergic blockade with phentolamine (△), and during β-adrenergic blockade with propranolol (○). Insulin was given immediately after basal sampling. R, acute autonomic reaction.

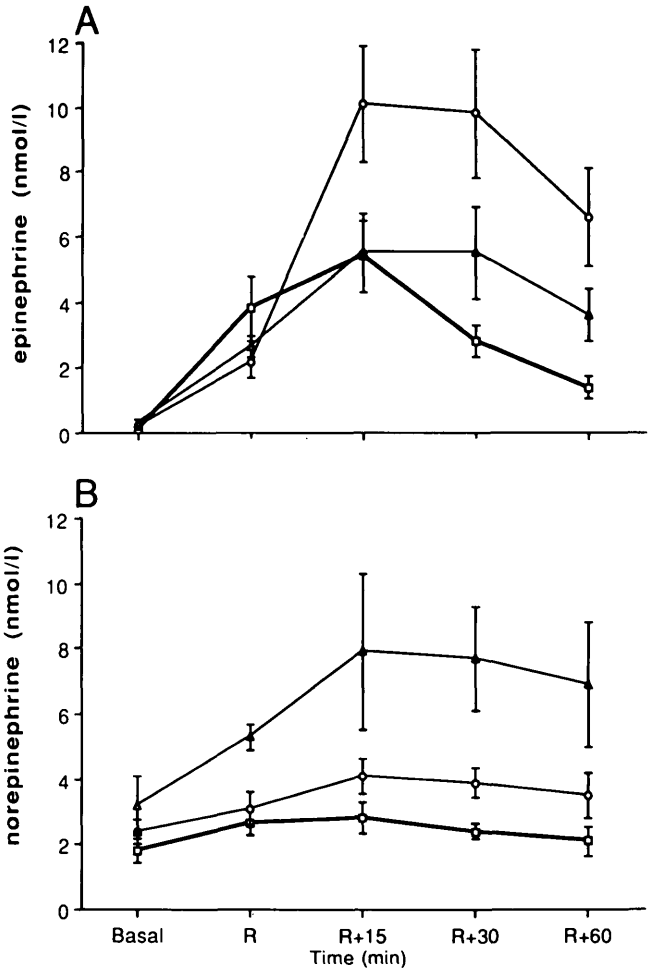

FIG. 3. Changes in plasma epinephrine (*A*) and norepinephrine (*B*) in response to insulin-induced hypoglycemia in control study (□), during α-adrenergic blockade with phentolamine (△), and during β-adrenergic blockade with propranolol (○). Insulin was given immediately after basal sampling. R, acute autonomic reaction.

Plasma epinephrine and norepinephrine concentrations increased significantly in response to hypoglycemia in the control group (Fig. 3). During α-adrenergic blockade with phentolamine, the epinephrine response was not significantly different compared with the control group, but the plasma norepinephrine concentration was significantly increased (ANOVA, $P < 0.05$). During β-blockade with propranolol, the plasma epinephrine concentrations were increased significantly compared with the control group (ANOVA, $P < 0.05$), whereas the norepinephrine responses were not significantly different (ANOVA, $P = 0.41$).

CONCLUSIONS

The effect of intravenous administration of insulin on lowering serum potassium has been used for many years as an emergency treatment for hyperkalemia. In this

study, the modest early decline in serum potassium concentration was not modified by either α- or β-adrenergic blockade, the latter confirming the results of a previous study in nondiabetic subjects with oral propranolol (3). This suggests that the initial fall in serum potassium occurs independently of adrenergic mechanisms and may represent a direct effect of insulin on the influx of potassium into cells (1).

The changes in serum potassium in response to hypoglycemia have been studied in tetraplegic patients with a traumatic transection of the cervical spinal cord producing a preganglionic sympathectomy (2). In these sympathectomized patients, activation of the sympathetic nervous system and secretion of catecholamines do not occur in response to hypoglycemia (13). The early fall in serum potassium was preserved, whereas the later decline in serum potassium after the onset of hypoglycemia was obtunded, suggesting mediation via adrenergic mechanisms (2). In this study, the later fall in serum potassium during hypoglycemia was inhibited by nonselective β-adrenergic blockade, whereas during nonselective α-adrenergic blockade an exaggerated fall in serum potassium occurred. This confirms and extends the observations of Petersen et al. (3), who demonstrated that the fall in serum potassium during hypoglycemia was abolished by β-adrenergic blockade with oral propranolol. The dose of propranolol used in this study would effectively block the clearance of epinephrine (14), which occurs by β-adrenergic mechanisms (15), and explains the higher concentration of plasma epinephrine in response to hypoglycemia with β-blockade. Despite a higher circulating epinephrine concentration, the fall in potassium in response to hypoglycemia was abolished, confirming mediation by β-adrenergic mechanisms (3).

A profound fall in potassium occurred in response to acute hypoglycemia during nonselective α-adrenergic blockade, and α-adrenoreceptor stimulation normally may inhibit the decrease in potassium, which is stimulated by β-adrenoreceptors, limiting the risk of severe hypokalemia developing in response to hypoglycemia. A similar physiological role for α-adrenoreceptor stimulation has been demonstrated in response to oral potassium (16) and potassium changes during exercise (17). In these situations, β-adrenergic stimulation enhances extrarenal potassium uptake, but α-adrenergic stimulation has the opposite effect. Alternatively, α-adrenoreceptor blockade causes an increase in the circulating concentration of norepinephrine by presynaptic blockade of α_2-receptors, which normally inhibit the release of norepinephrine (6,7), and this increased norepinephrine concentration may have stimulated β-receptors further and may have thereby provoked a greater fall in potassium, or this profound fall in serum potassium may have occurred secondary to the marked vasodilatation and increased perfusion of muscle, which accompanies α-blockade and the removal of α-induced vasoconstriction (18). Finally, studies in animals suggest that the liver has α-adrenergic receptors, the stimulation of which causes the release of potassium into the systemic circulation, and this may explain why α-blockade augments the hypoglycemia-induced hypokalemia (19).

Phentolamine is a nonselective α-adrenoreceptor blocker. α-Adrenoreceptors can be subdivided into α_1- and α_2-receptors (20). Selective pharmacological blockers of both of these receptor subgroups are now available (21). In particular, α_1-blockers may be implicated in the treatment of hypertension in diabetic subjects because of a beneficial effect on blood lipids (21). Although α-blocking drugs given orally may not have such a pronounced effect, the production of sudden severe hypokalemia could limit the role of α_1-blocking drugs in the treatment of hypertension in insulin-treated diabetic subjects. The latter are often exposed to episodes of hypoglycemia of the severity produced in this study and might experience dangerous and prolonged hypokalemia with the risk of cardiac arrhythmia (22). Further studies are required to determine whether this augmented fall in potassium in response to hypoglycemia is caused by α_1- or α_2-mechanisms before α_1-antagonists can be recommended with safety for subjects with insulin-treated diabetes.

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