Adrenergic Mechanisms for the Effects of Epinephrine on Glucose Production and Clearance in Man

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ABSTRACT The present studies were undertaken to assess the adrenergic mechanisms by which epinephrine stimulates glucose production and suppresses glucose clearance in man: epinephrine (50 ng/kg per min) was infused for 180 min alone and during either alpha (phentolamine) or beta (propranolol)-adrenergic blockade in normal subjects under conditions in which plasma insulin, glucagon, and glucose were maintained at comparable levels by infusion of somatostatin (100 μg/h), insulin (0.2 mU/kg per min), and variable amounts of glucose. In additional experiments, to control for the effects of the hyperglycemia caused by epinephrine, variable amounts of glucose without epinephrine were infused along with somatostatin and insulin to produce hyperglycemia comparable with that observed during infusion of epinephrine. This glucose infusion suppressed glucose production from basal rates of 1.8±0.1 to 0.0±0.1 mg/kg per min (P < 0.01), but did not alter glucose clearance. During infusion of epinephrine, glucose production increased transiently from a basal rate of 1.8±0.1 to a maximum of 3.0±0.2 mg/kg per min (P < 0.01) at min 30, and returned to near basal rates at min 180 (1.9±0.1 mg/kg per min). Glucose clearance decreased from a basal rate of 2.0±0.1 to 1.5±0.2 ml/kg per min at the end of the epinephrine infusion (P < 0.01). Infusion of phentolamine did not alter these effects of epinephrine on glucose production and clearance. In contrast, infusion of propranolol completely prevented the suppression of glucose clearance by epinephrine, and inhibited the stimulation of glucose production by epinephrine by 80±6% (P < 0.001). These results indicate that, under conditions in which plasma glucose, insulin, and glucagon are maintained constant, epinephrine stimulates glucose production and inhibits glucose clearance in man predominantly by beta adrenergic mechanisms.

INTRODUCTION

Epinephrine causes hyperglycemia in man by both increasing glucose production and decreasing glucose clearance (1–3). The adrenergic mechanisms responsible for these effects have not been established (4, 5). Assessment of these mechanisms in vivo is difficult because epinephrine may alter glucose production or clearance through a variety of actions. For example, increases in glucose production that occur during infusion of epinephrine may result in part from a direct effect of epinephrine on the liver (6) as well as from effects of epinephrine on insulin secretion (7), glucagon secretion (8), and gluconeogenic precursor availability (9). The decreases in glucose clearance observed during infusion of epinephrine may be due in part to direct inhibition of tissue glucose uptake by epinephrine (10–12) and to inhibition of tissue glucose uptake secondary to effects of epinephrine on plasma insulin (7) and free fatty acid concentrations (13). Furthermore, when assessment of these adrenergic mechanisms is attempted in vivo by infusing either an alpha or beta adrenergic antagonist along with epinephrine, alteration in circulating hormone and substrate concentrations (e.g., insulin and glucagon, or insulin and free fatty acids) occur that may have opposing effects on glucose production or clearance (2, 7, 14).

The current studies were, therefore, undertaken to evaluate the adrenergic basis for the effects of epinephrine on glucose production and glucose clearance in man under conditions that maintained the same plasma levels of insulin, glucagon, and glucose during infusion of epinephrine alone, epinephrine plus a beta adrenergic antagonist, and epinephrine plus an alpha adrenergic antagonist. Furthermore, the effects of the hypergly-
cemia caused by infusion of epinephrine were controlled by assessing, under the same conditions, the effects of hyperglycemia induced by infusion of glucose. The results of these experiments indicate that prolonged hyperglycemia has a continuing effect on both glucose production and glucose clearance, and that, under conditions in which plasma insulin and glucagon are maintained at constant levels, the stimulation of glucose production and the suppression of glucose clearance by epinephrine are predominantly the result of activation of beta adrenergic mechanisms.

METHODS

Informed written consent was obtained from five healthy female adult volunteers (aged 19–21 yr). All were within 10% of their ideal body weight (Metropolitan Life Insurance tables) and had no family history of diabetes mellitus. Subjects were admitted to the outpatient facility of the Mayo Clinic General Clinical Research Center, Rochester, Minn., between 7:00 and 8:00 a.m. after having fasted overnight (10–12 h). Four protocols, each of which was separated by at least 48 h, were employed. All subjects were studied on protocols A, B, and C; four of the subjects were studied on protocol D.

For each protocol, the subjects were placed at bed rest and maintained supine thereafter. An antecubital vein of one arm was cannulated with an 18-gauge catheter for infusion of hormones, isotope, and, in the case of protocols B, C, and D, glucose. A dorsal hand vein of the contralateral arm was cannulated with a 19-gauge “butterfly” needle for sampling of “arterialized venous” blood (15). The hand was kept in a heated box (60°C) throughout the experiment (15). For protocols B, C, and D, an additional 18-gauge catheter was placed in this arm for continuous blood withdrawn by a Biostator (Life Science Instruments, Elkhart, Ill.) for constant glucose monitoring. A primed (11 μCi) continuous (0.11 μCi/min) infusion of [3-3H]glucose (New England Nuclear, Boston, Mass., specific activity 17.54 Ci/M made up in 0.9% NaCl, 50 μCi/50 ml) was begun for isotopic determination of glucose appearance and disappearance rates; 2 h were allowed for isotopic equilibration before all experiments.

In all protocols, subjects were infused with somatostatin, 100 μg/h (courtesy of Dr. Jean Rivier and Dr. Roger Guillemin, Salk Institute, San Diego, Calif.), and crystalline insulin, 0.2 mU/kg per min (Eli Lilly & Co., Indianapolis, Ind.) from 0 through 180 min in order to maintain constant (and equivalent) plasma levels of insulin and glucagon under all experimental conditions. The initial study for all subjects was protocol A; in this protocol epinephrine (Parke Davis & Co., Detroit, Mich.) was infused at a rate of 50 ng/kg per min from 0 to 180 min. The order of the other protocols was varied. For protocol B, glucose (50 g/100 ml, see below) was infused from 0 through 180 min. For protocol C, epinephrine (50 ng/kg per min) plus propranolol (5 mg over 2 min followed by 80 μg/min, Ayerst, New York) were infused from 0 through 180 min. For protocol D, epinephrine (50 ng/kg per min) plus phentolamine (5 mg over 2 min followed by 500 μg/min, CIBA-Geigy Corp., Summit, N.J.) was infused from 0 through 180 min. During protocols B, C, and D, variable amounts of glucose (Table I) were infused via a syringe pump (Harvard Apparatus Co., Inc., Boston, Mass.) to “clamp” the plasma glucose levels at the same concentrations that had been observed during protocol A when epinephrine was infused. Depending on changes in plasma glucose concentration observed during continuous glucose monitoring, the necessary adjustments in the glucose infusion rate were made empirically.

All reagents were prepared on the morning of each experiment. Somatostatin and insulin were dissolved in 0.9% NaCl containing 1% human serum albumin (Cutter Laboratories, Berkeley, Calif.). Epinephrine (17 μg/ml) was dissolved in 0.9% NaCl containing ascorbic acid, 1 mg/ml (Eli Lilly & Co.). Propranolol (0.4 mg/ml) and phentolamine (2.4 mg/ml) were dissolved in 0.9% NaCl.

Blood samples were obtained at 15–30-min intervals throughout the experimental periods; samples for glucagon and insulin determination were collected in heparinized tubes containing 17 mg EDTA and 0.5 M benzamidine (Sigma Chemical Co., St. Louis, Mo.). Blood for plasma catecholamine determinations was collected in chilled heparinized tubes containing 20 mg reduced glutathione (Sigma Chemical Co.). Blood for plasma glucose and glucose specific activity was collected in NaF-oxalate tubes (Kimble-Terumo, Elkton, Md.); an aliquot of this plasma was used for determination of glucose concentration in duplicate (A23, Yellow Springs Instrument Co., Yellow Springs, Ohio); the remainder was aliquoted in triplicate (0.6 ml) and deproteinized by the addition of 0.1 ml chilled perchloric acid for subsequent determination of glucose radioactivity. All blood samples for hormone and substrate determination were centrifuged immediately after each experiment, and the resultant plasma was stored at −20°C until assay.

Plasma [3-H]glucose specific activity was determined as previously described (16); in brief, triplicate 0.3-ml aliquots of deproteinized plasma were evaporated to dryness at 37°C under compressed air to remove tritiated water. The residue was resuspended in 0.5 ml distilled water, and after the addition of 10 ml Aquasol (New England Nuclear), its radioactivity was counted in a refrigerated liquid scintillation spectrometer. Correction for quenching was made using the method of external standard ratios. The calculated infusion rate of the isotope was verified by measuring the volume of the [3-H]glucose solution before and after each experiment.

Plasma insulin (17) and glucagon (18; Unger 30K antibody) were determined by radioimmunoassay. Plasma catecholamines were assayed using a single isotope derivative method (19).

Rates of glucose appearance and disappearance were calculated employing the equations of Steele et al. (20) as modified by DeBodo et al. (21). Endogenous glucose production was obtained by subtracting the amount of glucose infused per 15-min interval from the total glucose production rate determined isotopically. Glucose clearance was calculated by dividing the rate of glucose disappearance by the appropriate plasma glucose concentration. The validity of the use of [3-H]glucose as a nonrecycling trace has been discussed in detail (22). For all calculations, it has been assumed that [3-H]glucose was not incorporated into glycogen and subsequently released. Data in text and figures are expressed as means ± SEM. Statistical significance was evaluated using two-tailed paired t test (23). Stable plasma glucose clamps were maintained from 90 through 180 min, and only data from this interval were employed for statistical analysis.

RESULTS

Effects of epinephrine infusion (Figs. 1 and 2, and Table I). Infusion of epinephrine at a rate of 50 ng/kg per min increased plasma epinephrine from a basal concentration of 26±4 pg/ml to levels averaging 882±60 pg/ml, from 90 through 180 min. Over this interval, plasma glucose increased from base-line values of 91±2 to a plateau of 149±10 mg/dl. Endogenous glucose production increased transiently from a basal rate of

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Mean ± SEM, see text for experimental details.

* Epi, epinephrine.
† Pro, propranolol.
‡ Phen, phentolamine.
1.8±0.1 to a maximum of 3.0±0.2 mg/kg per min at min 30, and then returned to approximately basal values (1.9±0.3 mg/kg per min) at min 180. Glucose clearance decreased progressively from a base-line rate of 2.0±0.1 to rates averaging 1.5±0.1 ml/kg per min, from 90 through 180 min (P < 0.01 vs. basal). Over this same interval, plasma glucagon decreased from a basal concentration of 134±37 pg/ml to values averaging 91±31 pg/ml (P < 0.01 vs. basal), while plasma insulin increased from a base-line level of 13±2 to values averaging 19±2 μU/ml (P < 0.01 vs. basal). Initial pulse rates of 75±2 increased to 84±3 beats/min at min 180 (P < 0.05).

Effects of glucose infusion (Figs. 1 and 2, and Table I). Variable amounts of glucose were infused in the absence of epinephrine to reproduce the plasma glucose levels observed during infusion of epinephrine. This was done to examine the effect of hyperglycemia per se on endogenous glucose production and glucose clearance. Over the interval from 90 to 180 min, plasma levels of glucose (149±9 mg/dl), insulin (20±2 μU/ml), and glucagon (95±41 pg/ml) were virtually identical to those observed during infusion of epinephrine. Plasma epinephrine remained at base-line levels (17–34 pg/ml) throughout. Endogenous glucose production (obtained by subtraction of the rate of exogenously infused glucose from total glucose appearance that was determined isotopically) was completely suppressed during the interval from 90 through 180 min, averaging 0.0±0.1 mg/kg per min compared with a basal rate of 1.8±0.1 mg/kg per min (P < 0.001). Glucose clearance from 90 through 180 min (1.9±0.1 ml/kg per min) was not different from basal values (2.0±0.1 ml/kg per min), but was significantly greater than those observed for the same interval during infusion of the epinephrine (1.5±0.1 ml/kg per min, P < 0.005).

Effects of beta adrenergic blockade during infusion of epinephrine (Figs. 2 and 3, and Table I). To evaluate the beta-adrenergic contribution to the effects of epinephrine on endogenous glucose production and

![FIGURE 1](image1.png)  
**FIGURE 1** Effect of epinephrine on endogenous glucose production and glucose clearance in the presence of constant plasma glucose, insulin, and glucagon concentrations. ●, epinephrine; ○, glucose. Mean±SEM; *, P < 0.05; n = 5.

![FIGURE 2](image2.png)  
**FIGURE 2** Plasma insulin, glucagon, and epinephrine during infusions of glucose alone, epinephrine alone, epinephrine plus propranolol, or epinephrine plus phentolamine. ○, glucose (n = 5); ●, epinephrine (n = 5); □, epinephrine + propranolol (n = 5); ■, epinephrine + phentolamine (n = 4). Mean±SEM; *, P < 0.05 vs. epinephrine.
glucose clearance, the beta adrenergic antagonist propranolol was infused along with epinephrine. Exogenous glucose was also infused at rates adjusted to maintain plasma glucose at the same concentrations as those observed during infusion of epinephrine without propranolol. During the interval from 90 through 180 min, plasma levels of glucose (148±8 mg/dl), insulin (22±3 μU/ml), and glucagon (91±35 pg/ml) were virtually identical to those observed over the same interval during infusion of epinephrine in the absence of propranolol. However, plasma epinephrine concentrations, when epinephrine was infused along with propranolol (2,142±137 pg/ml), were approximately threefold greater than those observed when epinephrine was infused without propranolol (P < 0.001). Endogenous glucose production decreased from a basal rate of 1.8±0.1 to 0.4±0.1 mg/kg per min during the interval from 90 through 180 min (P < 0.001); this rate was significantly less than that observed over the same interval during infusion of epinephrine without propranolol (P < 0.001) and represented a 81±6% suppression of epinephrine-stimulated glucose production. In contrast to the decrease in glucose clearance observed during infusion of epinephrine without propranolol, glucose clearance was unaltered during infusion of epinephrine in the presence of propranolol. Initial pulse rates of 67±6 beats/min decreased to 61±5 beats/min at min 180. In no subject was an increase in pulse rate observed during the experiment.

Effects of alpha adrenergic blockade during epinephrine infusion (Figs. 2 and 4, and Table 1). To evaluate the alpha adrenergic contribution to the effects of epinephrine on endogenous glucose production and glucose clearance, the alpha adrenergic antagonist phentolamine was infused along with epinephrine. Exogenous glucose was also infused at rates adjusted to maintain plasma glucose at the same concentrations as those observed during infusion of epinephrine without phentolamine. During the interval from 90 through 180 min, plasma levels of glucose (158±9 mg/dl), insulin (22±3 μU/ml), glucagon (101±42 pg/ml), and epinephrine (870±19 pg/ml) were not significantly different from those observed during the same interval when epinephrine was infused without phentolamine. During this interval, rates of endogenous glucose production and glucose clearance were also not significantly different from those observed over the same interval when epinephrine was infused without phentol-

**Figure 3** Effect of beta adrenergic blockade on epinephrine-induced changes in endogenous glucose production and glucose clearance in the presence of constant plasma glucose insulin and glucagon concentrations. ●, epinephrine alone; ○, epinephrine propranolol. Mean±SEM; *, P < 0.05; n = 5.

**Figure 4** Effect of alpha adrenergic blockade on epinephrine-induced changes in endogenous glucose production and glucose clearance in the presence of constant plasma glucose, insulin, and glucagon concentrations. ●, epinephrine alone; ○, epinephrine + phentolamine. Mean±SEM; *, P < 0.05; n = 4.
amine. Initial pulse rates of 73±3 beats/min increased to 105±7 beats/min at min 180 (P < 0.05).

DISCUSSION

The present studies were undertaken to examine the adrenergic mechanisms responsible for the stimulation of glucose production and the inhibition of glucose clearance observed during infusion of epinephrine in man. Propranolol and phenotamine were employed to induce, respectively, beta and alpha adrenergic blockade during infusions of epinephrine. In addition, somatostatin, insulin, and variable amounts of glucose were infused to maintain plasma insulin, glucagon, and glucose levels comparable under all experimental conditions. This was done because mere infusion of epinephrine during alpha and beta adrenergic blockade would result in differences in circulating insulin, glucagon, and glucose levels comparable under all experimental conditions. This was done because mere infusion of epinephrine during alpha and beta adrenergic blockade might make it difficult to draw definitive conclusions regarding the underlying adrenergic mechanisms. As a control for the hyperglycemia observed during infusion of epinephrine, the effects of hyperglycemia were examined by infusing glucose at rates appropriate to maintain plasma glucose levels similar to those observed during infusion of epinephrine.

Glucose infusion suppressed endogenous glucose production virtually to zero but did not alter glucose clearance. Infusion of epinephrine decreased glucose clearance ~30%. During infusion of epinephrine, glucose production increased transiently and returned to near basal rates, averaging 2.0±0.1 mg/kg per min over the last 90 min of the epinephrine infusion. Similar transient increases in glucose production have been observed during infusion of epinephrine in dogs (24, 25) and in man (1–3). These increases have been interpreted to indicate that the liver becomes refractory to prolonged hyperepinephrinemia (25). A similar conclusion would have been arrived at in the present studies if the suppressive effect of hyperglycemia itself had not been taken into consideration. The maintenance of basal rates of glucose production, during infusion of epinephrine in the presence of a degree of hyperglycemia that had completely suppressed glucose production when produced by an exogenous glucose infusion, indicates that prolonged hyperepinephrinemia continues to have an effect on the liver. A similar persistent effect of prolonged hyperglucagonemia on the liver has recently been demonstrated (26, 27); as with epinephrine, initial observations that prolonged infusion of glucagon caused only a transient increase in glucose production had suggested that glucagon had only a transient effect on the liver (28, 29).

In the present studies, infusion of phentolamine to induce alpha adrenergic blockade had no effect on either the stimulation of glucose production or the suppression of glucose clearance by epinephrine. In contrast, infusion of propranolol to induce beta adrenergic blockade completely reversed the suppressive effect of epinephrine on glucose clearance and caused nearly complete (~80%) reversal of the stimulatory effect of epinephrine on glucose production. These results indicate that, in the absence of epinephrine-induced changes in plasma insulin and glucagon, epinephrine increases glucose production and decreases glucose clearance in man predominantly by a beta adrenergic mechanism.

The lack of a complete reversal of the effects of epinephrine on glucose production during infusion of propranolol could be indicative of a 20% alpha adrenergic contribution to epinephrine-stimulated glucose production. Indeed, in vitro studies of rat liver (30, 31) have demonstrated that epinephrine can stimulate glucose production by both alpha and beta adrenergic mechanisms. On the other hand, in the present studies, the lack of complete reversal of the effects of epinephrine on glucose production by propranolol could simply have resulted from incomplete beta adrenergic blockade. Despite (a) the fact that the same doses of propranolol as those used in the present studies have been reported to completely block the beta adrenergic effects of epinephrine on plasma glycerol, lactate, and beta hydroxybutyrate levels (2), and (b) the lack of evidence in the present studies for incomplete beta adrenergic blockade based on observations of pulse rates, we favor the latter explanation rather than an alpha adrenergic contribution because, in the present studies, alpha adrenergic blockade had no measurable effect on the stimulation of glucose production by epinephrine. Moreover, recent studies employing the euglycemic-hyperinsulinenic clamp technique in man have indicated that all of the effect of epinephrine on glucose production could apparently be accounted for by a beta adrenergic mechanism (32).

The findings of the present study regarding a beta adrenergic mechanism for the suppression of glucose clearance by epinephrine are consistent with results from in vitro studies (10–11), indicating that the inhibition of muscle glucose uptake by epinephrine is reversed by beta adrenergic blockade. However, the present studies do not permit identification of the tissues whose clearance of glucose was affected by epinephrine or assessment of whether the effects of epinephrine were the result of a direct action on these tissues. It should be pointed out that under conditions in which plasma insulin and glucagon are not maintained at constant levels (as they were in the present study), infusion of epinephrine may decrease glucose clearance indirectly by preventing an increase in plasma insulin appropriate for the degree of concomitant hyperglycemia (2), and may also increase glucose production indirectly by stimulating glucagon secretion (8). Indeed,
under such conditions, when epinephrine is infused during beta adrenergic blockade with propranolol, there is a decrease in plasma insulin accompanied by only a modest diminution of the stimulation of glucose production by epinephrine, and no alteration in the suppression of glucose clearance by epinephrine (2). These results would lead to an underestimation of the beta adrenergic contribution to the stimulation of glucose production and suppression of glucose clearance by epinephrine because of alpha adrenergic inhibition of insulin release. The results of the present studies, interpreted in the context of the above observations, suggest that infusion of epinephrine primarily stimulates glucose production and suppresses glucose clearance by beta adrenergic mechanisms, and that these effects are augmented by the concomitant alpha adrenergic inhibitory effects of epinephrine on insulin secretion.

It is notable that during the infusion of epinephrine with propranolol, plasma epinephrine concentration rose to approximately threefold higher levels than those achieved during the infusion of epinephrine alone, suggesting that beta adrenergic blockade reduces the clearance of epinephrine from the circulation. This potentially important observation is being pursued in our laboratories. With respect to the present study, however, this finding does not detract from the interpretation of the data developed in the preceding paragraphs, because plasma epinephrine concentrations were higher during beta adrenergic blockade, a condition that completely blocked the suppressive effect of epinephrine on glucose clearance and that largely blocked the stimulatory effect of epinephrine on glucose production. Indeed, the higher plasma epinephrine concentration may explain the failure of beta adrenergic blockade to completely block the latter.

In conclusion, the present studies demonstrate in man (a) that prolonged hyperepinephrinemia has a persistent effect on glucose production as well as a sustained inhibitory effect on glucose clearance, and (b) that under conditions in which plasma glucose, insulin, and glucagon levels are maintained constant, the stimulation of glucose production and the suppression of glucose clearance by epinephrine is predominantly the result of beta adrenergic mechanisms.

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