

## Adrenergic Modulation of Pancreatic Glucagon Secretion in Man

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### Research Article

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The present studies thus confirm that catecholamines affect glucagon secretion in man and demonstrate that the pancreatic alpha cell possesses both alpha and beta adrenergic receptors. Beta adrenergic stimulation augments basal glucagon secretion, while alpha adrenergic stimulation diminishes basal glucagon secretion. Furthermore, since infusion of phentolamine, an alpha adrenergic antagonist, resulted in an elevation of basal plasma glucagon levels, there appears to be an [...]

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# Adrenergic Modulation of Pancreatic Glucagon Secretion in Man

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**ABSTRACT** In order to characterize the influence of the adrenergic system on pancreatic glucagon secretion in man, changes in basal glucagon secretion during infusions of pure alpha and beta adrenergic agonists and their specific antagonists were studied. During infusion of isoproterenol (3  $\mu\text{g}/\text{min}$ ), a beta adrenergic agonist, plasma glucagon rose from a mean ( $\pm\text{SE}$ ) basal level of  $104\pm 10$  to  $171\pm 15$   $\text{pg}/\text{ml}$ ,  $P < 0.0002$ . Concomitant infusion of propranolol (80  $\mu\text{g}/\text{min}$ ), a beta adrenergic antagonist, prevented the effects of isoproterenol, although propranolol itself had no effect on basal glucagon secretion. During infusion of methoxamine (0.5  $\text{mg}/\text{min}$ ), an alpha adrenergic agonist, plasma glucagon declined from a mean basal level of  $122\pm 15$  to  $75\pm 17$   $\text{pg}/\text{ml}$ ,  $P < 0.001$ . Infusion of phentolamine (0.5  $\text{mg}/\text{min}$ ), an alpha adrenergic antagonist, caused a rise in plasma glucagon from a mean basal level of  $118\pm 16$  to  $175\pm 21$   $\text{pg}/\text{ml}$ ,  $P < 0.0001$ . Concomitant infusion of methoxamine with phentolamine caused a reversal of the effects of phentolamine.

The present studies thus confirm that catecholamines affect glucagon secretion in man and demonstrate that the pancreatic alpha cell possesses both alpha and beta adrenergic receptors. Beta adrenergic stimulation augments basal glucagon secretion, while alpha adrenergic stimulation diminishes basal glucagon secretion. Furthermore, since infusion of phentolamine, an alpha adrenergic antagonist, resulted in an elevation of basal plasma glucagon levels, there appears to be an inhibitory alpha adrenergic tone governing basal glucagon secretion. The above findings suggest that catecholamines may influence glucose homeostasis in man through their effects on both pancreatic alpha and beta cell function.

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## INTRODUCTION

Considerable evidence indicates that catecholamines stimulate glucagon secretion in several species (1-5), including man (6). Furthermore, hyperglucagonemia has been reported to occur during certain stressful conditions (7-15) known to be associated with enhanced catecholamine release. These observations thus suggest that the adrenergic system exerts a physiologic influence over pancreatic alpha cell function and that some of the metabolic effects of catecholamines may be the result of altered glucagon secretion.

Recent studies (16-20) indicate that catecholamines may influence glucagon secretion in vivo through a neural mechanism. Since the natural neurohormone of the sympathetic system, norepinephrine, has affinity for both alpha and beta adrenergic receptors, the effects of this catecholamine may be mediated through activation of either receptor. In the rat (5) and in the dog (3, 14, 21), most studies indicate that catecholamines stimulate glucagon secretion by activation of beta adrenergic receptors, while in the duck (22) an alpha adrenergic mechanism has been reported.

In man, epinephrine, a catecholamine capable of activating both alpha and beta adrenergic receptors, has been shown to stimulate glucagon secretion (6). Although it is well established that catecholamines augment insulin secretion in man via beta adrenergic receptors and inhibit insulin secretion via alpha adrenergic receptors (23, 24), comparable studies of the receptor mechanism through which catecholamines affect human glucagon secretion have not been reported. The present investigation was therefore undertaken in order to characterize further the influence of the adrenergic system on pancreatic alpha cell function in man.

## METHODS

**Subjects.** 18 normal subjects (14 men and 4 women) between 22 and 34 yr of age were studied. None were obese

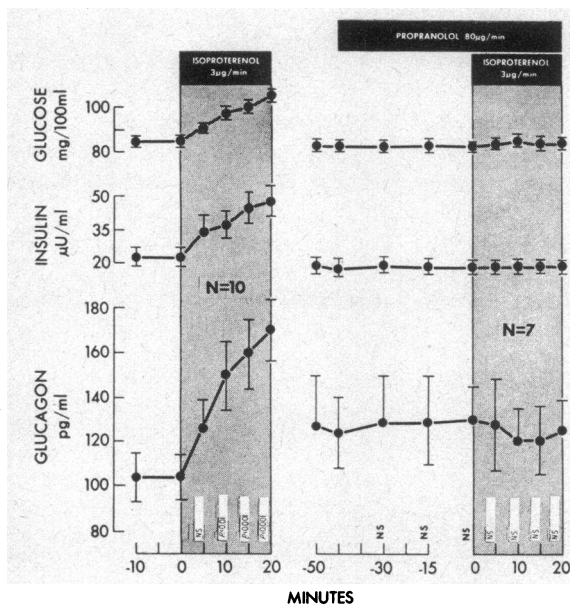


FIGURE 1 Effects of beta adrenergic stimulation (left) and inhibition (right) on basal plasma glucose, insulin, and glucagon levels. *P* vs. plasma glucagon at 0 min.

(weight 95–105% ideal body weight, according to the statistical tables of the Metropolitan Life Insurance Co.), and none had a family history of diabetes mellitus. The subjects were studied on several different occasions, since each served as his control. Each subject was instructed to maintain his usual eating habits. During the entire study period the weight of each subject was stable.

**Procedures.** Studies were begun between 7 and 8 a.m., after an 8–12-h overnight fast. Upon arrival at the research ward, subjects were put to bed, and slow intravenous infusions of 0.85% sodium chloride were begun in an antecubital vein of each arm. From one catheter blood samples were taken, and drugs were administered via the other. A 30-min equilibration period was allowed before initiating any studies.

All adrenergic agents were administered after appropriate dilution in 0.85% sodium chloride by controlled infusion via a Harvard pump apparatus (Harvard Apparatus Co., Inc., Millis, Mass.). Isoproterenol (Isuprel, Winthrop Laboratories, New York) was infused at a rate of 3 µg/min for 20 min in order to ascertain the effects of beta adrenergic stimulation. Propranolol (Inderal, Ayerst Laboratories, New York) was infused at a rate of 80 µg/min for 65 min in order to study the effects of beta adrenergic receptor inhibition. Methoxamine (Vasoxyl, Burroughs Wellcome Co., Research Triangle Park, N. C.) was infused at a rate of 0.5 mg/min for 20 min in order to ascertain the effects of alpha adrenergic stimulation. Phentolamine (Regitine, Ciba Pharmaceutical Co., Summit, N. J.) was infused for 65 min in order to study the effects of alpha adrenergic receptor inhibition. When the effects of an adrenergic inhibitor upon an adrenergic stimulator were studied, the inhibitor was infused for 45 min before and during the infusion of the stimulator.

**Determinations.** Blood specimens for measurement of plasma glucose (25), insulin (26), and glucagon (27) levels were collected in chilled plastic syringes. Specimens for

plasma glucagon were dispensed into tubes on ice containing 12 mg EDTA and 0.5 M benzamidine (28). Upon completion of experiments, tubes were immediately centrifuged at 4°C for 15 min and then stored at –20°C until assay, not more than 4 wk later. Glucagon immunoassay was performed as previously described (27) using antiserum 30K (purchased from the Diabetes Research Fund, University of Texas Southwestern Medical School at Dallas) which is highly specific for pancreatic glucagon. When using this antiserum, plasma glucagon was undetectable in a totally pancreatectomized patient. For plasma values between 100 and 200 pg/ml the interassay coefficient of variation is 15% and the intrassay coefficient is 10%. The minimal sensitivity of the assay using 0.2 ml plasma is 25 pg/ml.

**Statistics.** Analysis of all data for statistical significance was performed using a two-tailed paired *t* test.

## RESULTS

**Effect of beta adrenergic stimulation and inhibition on basal glucagon and insulin secretion (Fig. 1).** Isoproterenol, a beta adrenergic agonist, was infused at a rate of 3 µg/min for 20 min (Fig. 1, left). Plasma glucagon rose progressively from a mean (±SE) basal level of 105±10 to 171±15 pg/ml at 20 min, *P* < 0.0002. This occurred despite significant concurrent elevations of plasma glucose and plasma insulin levels. During this interval, plasma glucose rose from a mean (±SE) basal level of 85±2 to 106±4 mg/100 ml at 20 min, *P* < 0.001, and plasma insulin rose from a mean (±SE) level of 23±3 to 48±8 µU/ml at 20 min, *P* < 0.002.

Propranolol, a specific beta adrenergic antagonist, was infused at a rate of 80 µg/min for 65 min (Fig. 1, right). During the initial 45 min, observations were made to ascertain whether beta adrenergic tone contributed to basal glucagon and insulin secretion. During the subsequent 20 min, isoproterenol (3 µg/min) was also infused to determine whether its previously observed effects could be prevented by prior beta adrenergic receptor blockade. During infusion of propranolol alone, no changes occurred in plasma glucose, insulin, and glucagon, indicating the absence of significant beta adrenergic tone. Similarly, during infusion of isoproterenol along with propranolol, no changes were observed in plasma glucose, insulin, and glucagon levels. Thus, propranolol prevented the effects of isoproterenol. This strongly suggests that the previous elevation of plasma glucose, insulin, and glucagon levels observed with isoproterenol had been due specifically to beta adrenergic stimulation.

**Effects of alpha adrenergic stimulation and inhibition on basal glucagon and insulin secretion (Fig. 2).** Methoxamine, an alpha adrenergic agonist, was infused at a rate of 0.5 mg/min for 20 min (Fig. 2, left). Plasma glucagon declined from a mean (±SE) basal level of 122±15 to a nadir of 75±17 pg/ml at 15 min, *P* < 0.001. No change in plasma insulin levels were observed. Plasma glucose rose slightly from a mean

( $\pm$ SE) basal level of  $84 \pm 2$  to  $90 \pm 3$  mg/100 ml at 20 min,  $P < 0.03$ . The change in plasma glucagon did not appear to be secondary to the rise in plasma glucose, since glucagon levels had declined significantly before any change in plasma glucose occurred.

Phentolamine, a specific alpha adrenergic antagonist, was infused at a rate of 0.5 mg/min for 65 min (Fig. 2, right). During the initial 45 min, observations were made to ascertain whether alpha adrenergic tone contributed to basal glucagon and insulin secretion. During the subsequent 20 min, methoxamine (0.5 mg/min) was also infused to determine whether its previously observed effects could be prevented by prior alpha adrenergic receptor blockade. During infusion of phentolamine alone, plasma glucagon rose from a mean ( $\pm$ SE) basal level of  $118 \pm 16$  to  $175 \pm 21$  pg/ml after 45 min,  $P < 0.0001$ . Plasma insulin rose from a mean ( $\pm$ SE) basal level of  $16 \pm 2$  to  $27 \pm 3$   $\mu$ U/ml after 45 min,  $P < 0.005$ . Despite these hormonal changes, no alteration in plasma glucose levels was observed. These results thus suggest an inhibitory alpha adrenergic tone on basal glucagon and insulin secretion.

When methoxamine (0.5 mg/min) was infused in addition to phentolamine, both plasma glucagon and plasma insulin levels declined ( $P < 0.002$ ) to basal levels. Plasma glucose remained unchanged. Although the inhibitory effects of methoxamine on glucagon secretion were not completely prevented by phentolamine, plasma glucagon did not fall below basal levels as had occurred with methoxamine alone. The decline in plasma glucagon after the addition of methoxamine occurred without any change in plasma glucose and thus must have been due either to a direct alpha adrenergic inhibitory effect on the pancreatic alpha cell or to some other metabolic effect of methoxamine.

## DISCUSSION

Although there is considerable evidence that catecholamines influence glucagon secretion (1-6, 16-22), the precise receptor mechanisms involved in man have not been defined. The present investigation was therefore undertaken to characterize the manner in which the adrenergic system influences human pancreatic alpha cell function. For this purpose, the effects of adrenergic agents and their specific antagonists, alone and in combination, were studied.

Isoproterenol, a beta adrenergic agonist, was found to elevate plasma glucagon levels from a mean basal concentration of  $104 \pm 10$  to  $171 \pm 15$  pg/ml. Plasma glucose and insulin levels also rose during infusion of isoproterenol, most likely because of direct beta adrenergic effects on liver glycogenolysis (29) and pancreatic beta cell function (23, 24). However, since glucagon can stimulate glycogenolysis (30) and insulin

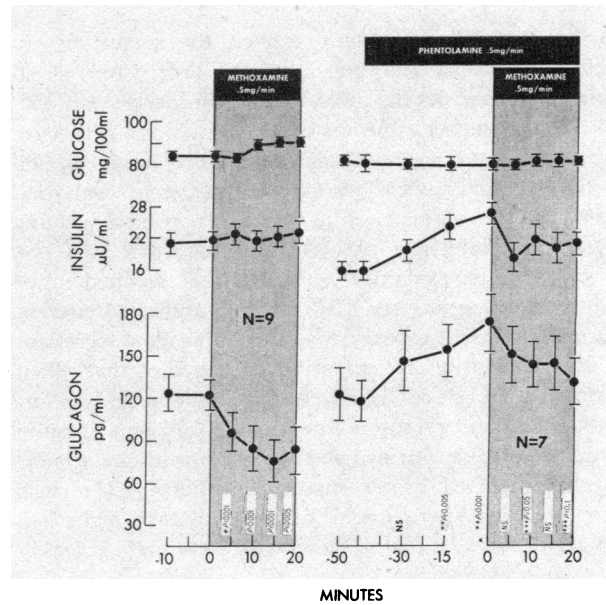


FIGURE 2 Effects of alpha adrenergic stimulation (left) and inhibition (right) on basal plasma glucose, insulin, and glucagon levels.  $P$  vs. plasma glucagon at 0 min (\*), -45 min (\*\*), and 0 min (\*\*\*)

secretion (31), a contributory effect of the associated hyperglucagonemia cannot be excluded. Since propranolol, a specific beta adrenergic antagonist, prevented the rise in plasma glucagon as well as the other responses seen during infusion of isoproterenol, it would thus appear that beta adrenergic stimulation augments glucagon secretion in man. However, since propranolol itself had no effect on plasma glucagon levels, one may conclude that there is little, if any, beta adrenergic tone-modifying pancreatic alpha cell function under basal conditions.

The rise in plasma glucagon levels caused by isoproterenol is comparable in magnitude to those observed in man during infusion of epinephrine (6) or alanine (32). Moreover, similar changes in plasma glucagon levels have also been reported in man during infection (7), myocardial infarction (10), exercise (11), 72-h fasts (33), and some instances of ketoacidosis (34), conditions generally acknowledged to be associated with heightened sympathetic nervous system activity. It is thus possible that the hyperglucagonemia seen in these situations may, in part, represent the effect of endogenous catecholamines.

Methoxamine, an alpha adrenergic agonist, diminished plasma glucagon levels from a mean basal concentration of  $122 \pm 15$  to  $75 \pm 17$  pg/ml. Although plasma insulin levels did not change, plasma glucose rose slightly (6 mg/100 ml). The fall in plasma glucagon cannot be attributed to this slight hyperglycemia, since plasma glucagon levels declined before any change in

plasma glucose occurred. Moreover, the magnitude of decline in plasma glucagon is of the order seen when plasma glucose levels are elevated in excess of 150 mg/100 ml during infusion of glucose (35). Although one might have expected plasma glucose levels to fall in the present study when plasma glucagon levels declined in the absence of a change in plasma insulin (36), the slight rise in plasma glucose that was observed may be explained as a result of methoxamine-induced glycogenolysis (37). Thus alpha adrenergic stimulation itself appears to inhibit glucagon secretion.

This conclusion is supported by the fact that when phentolamine, an alpha adrenergic antagonist, was infused, plasma glucagon levels rose. Plasma insulin levels also rose during phentolamine infusion similar to that reported by Robertson and Porte (24), who proposed that there might be an inhibitory alpha adrenergic tone on basal pancreatic beta cell function. The present findings support this concept and further suggest that there is an inhibitory alpha adrenergic tone modulating basal glucagon secretion in man. Although one may have expected a rise in plasma glucagon to be associated with a rise in plasma glucose (30), in both the present study and that of Robertson and Porte (24), plasma glucose levels did not change during infusion of phentolamine. This might have occurred because of offsetting effects of concomitant hyperinsulinemia and hyperglucagonemia.

When methoxamine infusion was superimposed upon infusions of phentolamine, the elevated plasma glucagon and insulin levels declined toward basal levels. Thus, phentolamine did not prevent methoxamine from having a suppressive effect on glucagon secretion. This may have been due to the inadequacy of the doses of phentolamine employed to block both endogenous and exogenous alpha adrenergic activity. Alternatively these results would be consistent with methoxamine-induced suppression of glucagon secretion occurring via a non-alpha adrenergic mechanism. However, this appears unlikely, since methoxamine possesses little intrinsic activity other than that of an alpha adrenergic agonist (38). Thus, the present study provides three lines of evidence in support of an inhibitory alpha adrenergic effect on glucagon secretion: (a) diminution of plasma glucagon levels during infusion of methoxamine, (b) augmentation of plasma glucagon levels during infusion of phentolamine, and (c) reversal of the effects of phentolamine by methoxamine.

The present studies indicate, therefore, that the human pancreatic alpha cell possesses both alpha and beta adrenergic receptors. Iversen (3) has previously reported that epinephrine, norepinephrine, and isoproterenol stimulated glucagon release from the isolated perfused canine pancreas; the effects of these agents

were abolished or markedly inhibited by pretreatment with propranolol. This suggests that a beta adrenergic mechanism was involved in stimulation of glucagon secretion and thus supports the findings of the present study in man. However, no evidence for the presence of alpha adrenergic receptors was found by Iversen in the dog. The limited number of experiments dealing with each alpha adrenergic agent, as well as the large variations among individual animals, may have been responsible for this conclusion. Evidence in favor of the presence of both alpha and beta adrenergic receptors in the dog was found by Lindsey and Faloon (14), who reported that administration of phentolamine augments canine glucagon responses to exsanguination and that propranolol diminishes glucagon responses. Moreover, although there are conflicting data in the rat (39, 5), studies of Luyckx and Le Fefevre (5) also support the present findings in man.

It is noteworthy that although the biologic effects of glucagon and insulin are antagonistic (40), pure alpha or beta adrenergic stimulation appears to affect pancreatic alpha and beta cell secretion similarly (3). However, *in vivo*, there are no naturally occurring pure alpha or beta adrenergic agents. Consequently one need not necessarily find parallel glucagon and insulin responses to native catecholamines. Thus, it has been shown (6) that epinephrine, a mixed adrenergic agent, enhances glucagon secretion while inhibiting insulin release in man. Since inhibition of insulin release by epinephrine is mediated by alpha adrenergic receptors, and stimulation of glucagon secretion occurs via beta adrenergic receptors (23, 24, 3), a likely explanation for this observation is that epinephrine causes predominant activation of alpha receptors on the pancreatic beta cell while it activates predominantly beta receptors on the pancreatic alpha cell. Evidence in support of this conclusion is provided by recent studies (41) showing that epinephrine lowers cyclic AMP (c-AMP) levels in pancreatic beta cells and simultaneously raises c-AMP levels in pancreatic alpha cells.

The differential effect of catecholamines on insulin and glucagon secretion may have important clinical implications, since the natural sympathetic neurohormone, norepinephrine, is capable of activating both alpha and beta adrenergic receptors. Modulation of pancreatic islet cell function by the adrenergic system would be advantageous in circumstances where there is an augmented demand for endogenous nutrients, such as during exercise or hypoglycemia. Inhibition of insulin release and stimulation of glucagon secretion by catecholamines would facilitate mobilization of stored substrate from triglyceride (42) and glycogen depots (30) and would provide the organism with additional metabolic fuels. Conversely, under other circumstances,

adrenergic effects on insulin and glucagon secretion may be deleterious (43). Further diminution of insulin secretion with a concomitant enhanced release of glucagon due to catecholamines would tend to exaggerate any adverse effects that might result solely from a slight impairment of insulin secretion. Thus, an adrenergic-induced imbalance of pancreatic alpha and beta cell function might provide an additional explanation for the deterioration of glucose homeostasis and catabolism seen during severe infections, burns, trauma, and myocardial infarction situations in which there is enhanced sympathetic activity and hyperglucagonemia (7, 8, 10).

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