

Adrenergic Receptor Control Mechanism for Growth Hormone Secretion

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ABSTRACT The influence of catecholamines on growth hormone secretion has been difficult to establish previously, possibly because of the suppressive effect of the induced hyperglycemia on growth hormone concentrations. In this study, an adrenergic receptor control mechanism for human growth hormone (HGH) secretion was uncovered by studying the effects of alpha and beta receptor blockade on insulin-induced growth hormone elevations in volunteer subjects.

Alpha adrenergic blockade with phentolamine during insulin hypoglycemia, 0.1 U/kg, inhibited growth hormone elevations to 30–50% of values in the same subjects during insulin hypoglycemia without adrenergic blockade. More complete inhibition by phentolamine could not be demonstrated at a lower dose of insulin (0.05 U/kg). Beta adrenergic blockade with propranolol during insulin hypoglycemia significantly enhanced HGH concentrations in paired experiments. The inhibiting effect of alpha adrenergic receptor blockade on HGH concentrations could not be attributed to differences in blood glucose or free fatty acid values; however, more prolonged hypoglycemia and lower plasma free fatty acid values may have been a factor in the greater HGH concentrations observed during beta blockade. In the absence of insulin induced hypoglycemia, neither alpha nor beta adrenergic receptor blockade had a detectable

effect on HGH concentrations. Theophylline, an inhibitor of cyclic 3'5'-AMP phosphodiesterase activity, also failed to alter plasma HGH concentrations.

These studies demonstrate a stimulatory effect of alpha receptors and a possible inhibitory effect of beta receptors on growth hormone secretion.

INTRODUCTION

Many of the stimuli for growth hormone secretion such as physical and surgical stress (1, 2), psychic stress (2), exercise (2), 2-deoxyglucose (1), hypoglycemia (1), histamine (3), vasopressin (4), and pyrogen (5) result in increased catecholamine concentrations in blood and tissues (2, 6–10). The control of pituitary growth hormone secretion by the hypothalamus is now widely accepted and recent evidence has shown that at least one of the above mentioned stimuli caused a discharge of growth hormone-releasing factor from the hypothalamus (11). As the catecholamine content of the hypothalamus is higher than that of any other central nervous system structure (12), the possibility that the effect of these stimuli on growth hormone secretion may be mediated by catecholamines must be considered.

The role of epinephrine in the control of growth hormone secretion has been controversial. Two groups of investigators (13, 14) have detected a stimulatory effect of epinephrine on growth hormone secretion while other investigators have been unable to demonstrate elevated growth hormone concentrations after epinephrine administration (2, 6, 15, 16). Perhaps epinephrine-induced hyperglycemia masked a stimulatory effect of the hormone on growth hormone secretion in the

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negative studies since hyperglycemia suppresses plasma growth hormone concentrations (1).

The present investigation was performed (a) to determine the effect of catecholamines on growth hormone secretion under conditions in which hyperglycemia could not mask a stimulatory effect, (b) to characterize any observed effect in terms of alpha and beta adrenergic receptors, and (c) to assess the role of endogenous catecholamines on the plasma growth hormone response to insulin hypoglycemia. Administration of alpha and beta adrenergic blocking agents during insulin hypoglycemia to determine their effect on plasma human growth hormone (HGH) elevations proved a suitable experimental design for these purposes.

METHODS

21 apparently healthy young male volunteers, 18–35 yr old, were selected for this study. Volunteers were excluded if they were obese (10% or more above ideal weight) or if they had a family history of diabetes. Two intravenous insulin tolerance tests were performed on the majority of the subjects: a control test in which glucagon-free insulin was given alone and another test in which insulin was given while the patient was receiving either an alpha or a beta adrenergic blocking agent. Several subjects had three insulin tolerance tests, a control test and one with each of the adrenergic blocking agents, and some subjects received the adrenergic blocking agents without insulin. The series of tests on each subject was performed in random order and was completed within a 10 day period. With few exceptions, at least 1 day intervened between tests. A total of 52 studies was performed on these 21 individuals.

The subjects were instructed to abstain from smoking and to take nothing by mouth except water at 10 p.m. the night before the study. Each subject reported to the room used for clinical testing at 7 a.m. After the subject had been weighed, he was put to bed and a slow intravenous infusion of 0.85% NaCl was begun through a 20 gauge needle in an antecubital vein. The indwelling needle was used for withdrawal of blood samples as well as for injections of insulin and drugs. The needle was kept open by the saline infusion and no anticoagulants were given to the subject or were present in the sampling syringes. A sphygmomanometer was placed on the opposite arm to monitor blood pressure. Blood pressure and pulse rate were taken every 15 min throughout the experiment.

After a 30 min base line period, glucagon-free insulin (0.05 or 0.1 U/kg) was injected. With the exception of the first 15 min interval after insulin injection, blood samples were taken every 15 min during the control period and for 90 min after the insulin had been given. In the alpha adrenergic blockade experiments, phentolamine was infused at a rate of 0.5 mg/min by a Sage constant infusion pump beginning immediately before insulin

administration and continuing throughout the remaining 90 min of the experiment. In the beta adrenergic blockade experiments, a "stat" dose of propranolol, 3 mg, was given intravenously and a constant infusion of propranolol at a rate of 0.08 mg/min was started immediately before insulin administration and was continued until the end of the experiment. Propranolol was not given to any subject with a resting pulse below 60 beats/min. On this basis, three subjects for whom propranolol experiments had been planned were rejected for that part of the study. In 11 studies (4 with alpha blockade and 7 with beta blockade) adrenergic blocking agents were given as described above, but without insulin. In four subjects, 500 mg of theophylline ethylenediamine was infused at a constant rate for 15 min at the end of the base line period. Blood samples were taken in all studies at the same intervals as in the experiments in which insulin was given.

Blood samples were collected in chilled heparinized tubes. Protein-free filtrates for blood glucose were made from 0.2 ml of blood immediately after the blood had been obtained. Blood glucose was determined by a glucose oxidase method (17). Plasma free fatty acid (FFA) was measured by a modification of the Dole procedure on 1-ml aliquots of plasma (18).

Plasma HGH was determined by a modification of the radioimmunoassay method of Schalch and Parker (19) utilizing ^{125}I -labeled growth hormone and separating free from bound hormone by the double antibody technique. Tracer and standards were prepared from highly purified HGH (Lot HS 968C) supplied to us by Dr. A. E. Wilhelmi. HGH antiserum was generously supplied by the National Institute of Arthritis and Metabolic Diseases and the National Pituitary Agency.

Propranolol (Inderal) was kindly supplied by Ayerst Laboratories, New York. Phentolamine (Regitine) and theophylline ethylenediamine (Aminophylline) were purchased from CIBA Pharmaceutical Products, Inc., Sum-

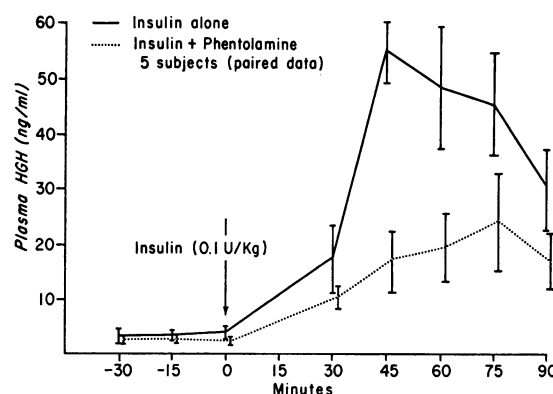


FIGURE 1 Effect of alpha adrenergic blockade on plasma human growth hormone (HGH) concentrations during insulin-induced hypoglycemia, 0.1 U/kg. Alpha adrenergic blockade was produced by phentolamine infusion (0.5 mg/min) begun at the time of insulin administration and continued throughout the remainder of the experiment. Means \pm SEM are shown.

mit, N. J. and the G. D. Searle & Co., Skokie, Ill., respectively.

RESULTS

Alpha adrenergic blockade during insulin hypoglycemia. The data shown in Fig. 1 demonstrate an inhibitory effect of alpha adrenergic blockade on plasma HGH concentrations during insulin hypoglycemia. Base line plasma HGH concentrations during the 30 min base line period were slightly higher in these and subsequent studies ($3.1 \pm .2$ m μ g/ml) than those usually reported for overnight fasting male subjects (1). Our subjects were ambulatory before testing which may partially account for the higher plasma HGH concentrations. Glucagon-free insulin administration, 0.1 U/kg, resulted in peak plasma HGH concentrations at 45–75 min after injection. In the same subjects during a phentolamine infusion, 0.5 mg/min, plasma HGH response to hypoglycemia was only one-third to one-half as great as in the experiment with insulin alone. Plasma HGH values were significantly different at the 45 and 60 min intervals with P values < 0.01 and < 0.02 , respectively (paired t test). Blood glucose and plasma FFA data for these experiments are expressed as per cent of pretest values (Fig. 2). Hypoglycemia

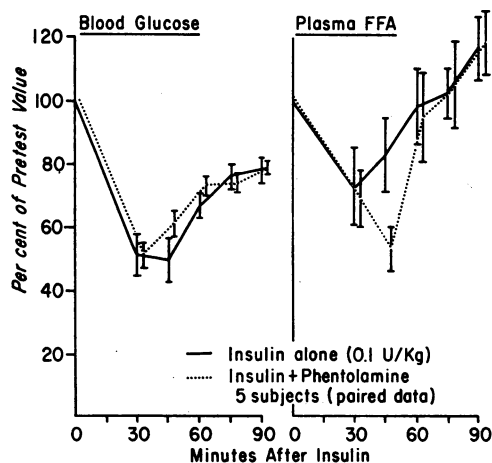


FIGURE 2 Effect of alpha adrenergic blockade on blood glucose and plasma FFA during insulin-induced hypoglycemia, 0.1 U/kg. Mean pretest blood glucose values were 74 ± 5.3 mg/100 ml and 77 ± 1.5 mg/100 ml in the insulin alone and alpha adrenergic blockade experiments, respectively. Mean pretest plasma FFA values were 690 ± 50 μ Eq/liter and 780 ± 60 μ Eq/liter in the insulin alone and alpha adrenergic blockade experiments, respectively. Means \pm SEM are shown.

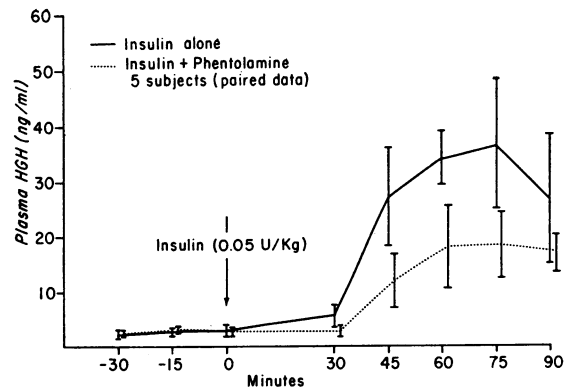


FIGURE 3 Effect of alpha adrenergic blockade on plasma HGH concentrations during insulin-induced hypoglycemia, 0.05 U/kg. Alpha adrenergic blockade produced as stated in Fig. 1. Means \pm SEM are shown.

was slightly more prolonged in the experiments with insulin alone but analysis of individual subject responses indicated that the greater plasma HGH elevation with insulin alone could not be attributed to this small difference. The plasma FFA difference 45 min after insulin injection can not be explained. As phentolamine alone was shown to lower plasma FFA in three of four subjects (Fig. 9) some enhancement of insulin-

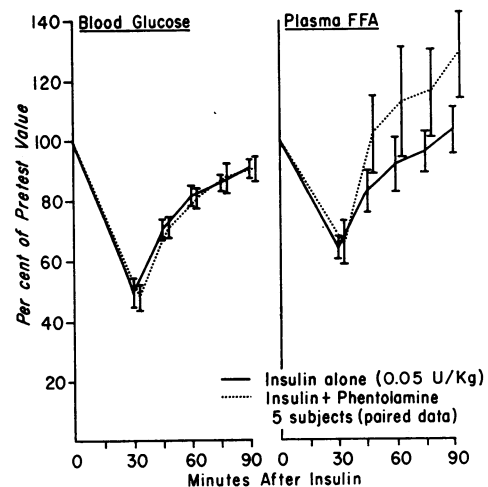


FIGURE 4 Effect of alpha adrenergic blockade on blood glucose and plasma FFA during insulin-induced hypoglycemia, 0.05 U/kg. Mean pretest blood glucose values were 79 ± 1.7 mg/100 ml and 77 ± 2.6 mg/100 ml in the insulin alone and alpha adrenergic blockade experiments, respectively. Mean pretest plasma FFA values were 607 ± 60 μ Eq/liter and 632 ± 32 μ Eq/liter in the insulin alone and alpha adrenergic blockade experiments, respectively. Means \pm SEM are shown.

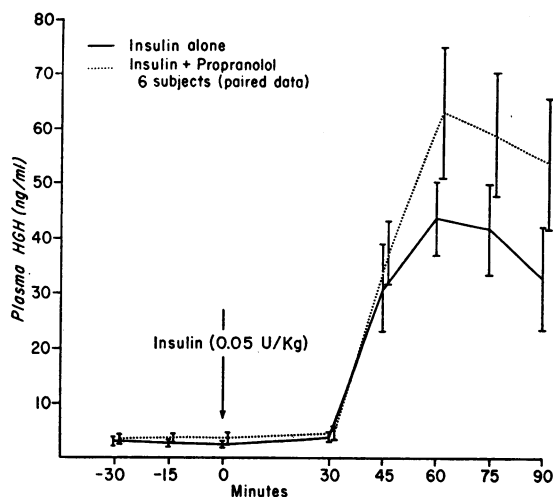


FIGURE 5 Effect of beta adrenergic blockade on plasma HGH concentrations during insulin-induced hypoglycemia, 0.05 U/kg. Beta adrenergic blockade was produced by a stat injection of 3 mg propranolol immediately before insulin administration followed by a constant propranolol infusion of 0.08 mg/min until termination of the experiment. Means \pm SEM are shown.

induced FFA depression by phentolamine may have occurred.

Similar alpha adrenergic blockade experiments were performed on five additional subjects during hypoglycemia produced by a smaller amount of insulin (0.05 U/kg) to determine if more complete

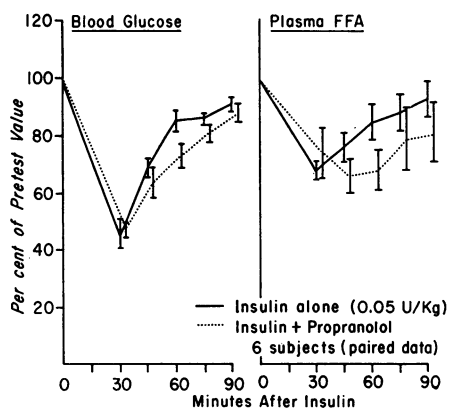


FIGURE 6 Effect of beta adrenergic blockade on blood glucose and plasma FFA during insulin-induced hypoglycemia, 0.05 U/kg. Mean pretest blood glucose values were 84 ± 7 mg/100 ml and 80 ± 1.8 mg/100 ml in the insulin alone and alpha adrenergic blockade experiments, respectively. Mean pretest plasma FFA values were 670 ± 88 μ Eq/liter and 557 ± 64 μ Eq/liter in the insulin alone and alpha adrenergic blockade experiments. Means \pm SEM are shown.

inhibition of the HGH response could be achieved. The smaller dose of insulin resulted in a lesser plasma HGH response (Fig. 3) and although complete inhibition was not achieved in any subject, phentolamine again depressed the growth hormone response. Plasma HGH values were significantly different at 45 and 60 min with P values < 0.05 (paired t test). Blood glucose and plasma FFA values for these experiments are shown in Fig. 4. As blood glucose concentrations with and without phentolamine were nearly identical, the possibility that differences in blood glucose could account for the inhibition of HGH response by phentolamine was eliminated. Plasma FFA in experiments with insulin alone and those with insulin and phentolamine reached the same nadir but a more rapid and higher rebound in plasma FFA occurred in the latter experiments. Because of the failure of the lower dose of insulin (0.05 U/kg) to elicit a HGH response in 3 of 10 volunteers, the effect of alpha adrenergic blockade on HGH response at an even lower insulin dose was not studied.

Beta adrenergic blockade during insulin hypoglycemia. Paired experiments in which six volunteers received insulin, 0.05 U/kg, with and without beta adrenergic blockade showed moderate enhancement of plasma HGH concentrations during beta adrenergic blockade with propranolol (Fig. 5). The sum of plasma HGH concentrations at 60, 75, and 90 min after insulin injection was

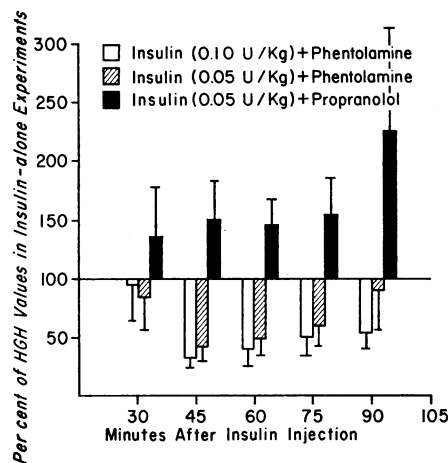


FIGURE 7 Effect of alpha and beta adrenergic blockade on plasma HGH response to insulin hypoglycemia. Means \pm SEM are shown.

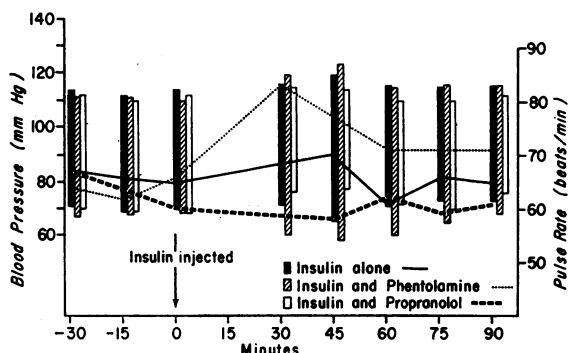


FIGURE 8 Effect of alpha and beta adrenergic blockade on pulse and blood pressure response to insulin-induced hypoglycemia, 0.05 U/kg.

significantly greater ($P < 0.02$) in the experiments with insulin and propranolol than in those with insulin alone. Hypoglycemia and plasma FFA depression were more prolonged during beta adrenergic blockade (Fig. 6) and a possible role of these factors in the greater HGH response cannot be excluded.

Summation of effects of adrenergic blockade on plasma HGH elevations and cardiovascular response to insulin hypoglycemia. Fig. 7 summarizes the effects of adrenergic receptor blockade on hypoglycemia-induced plasma HGH elevations. In

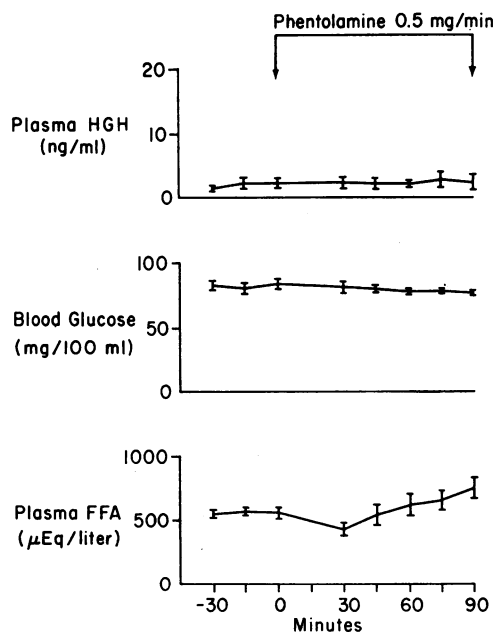


FIGURE 9 Effect of alpha adrenergic blockade with phentolamine on plasma HGH, blood glucose, and plasma FFA in four normal subjects. Means \pm SEM are shown.

the presence of alpha adrenergic blockade, maximal inhibition of plasma HGH elevations to 30–50% of values in experiments with insulin alone occurred at 45 and 60 min after insulin administration. During beta adrenergic blockade, HGH response was approximately 50% greater than in experiments with insulin alone at each time period except for an even greater increase at 90 min.

The cardiovascular responses to insulin hypoglycemia during either alpha or beta adrenergic blockade are shown in Fig. 8. The increase in pulse rate and pulse pressure during insulin hypoglycemia is accentuated by alpha receptor blockade with phentolamine and inhibited by beta receptor blockade with propranolol.

Alpha and beta adrenergic blockade in the absence of insulin hypoglycemia. Neither alpha adrenergic blockade (Fig. 9) nor beta adrenergic blockade (Fig. 10) had a detectable effect on plasma HGH concentrations in the absence of insulin hypoglycemia. An initial fall in plasma FFA occurred during phentolamine infusion (Fig. 9) whereas minimal if any depression of plasma FFA occurred during propranolol infusion (Fig.

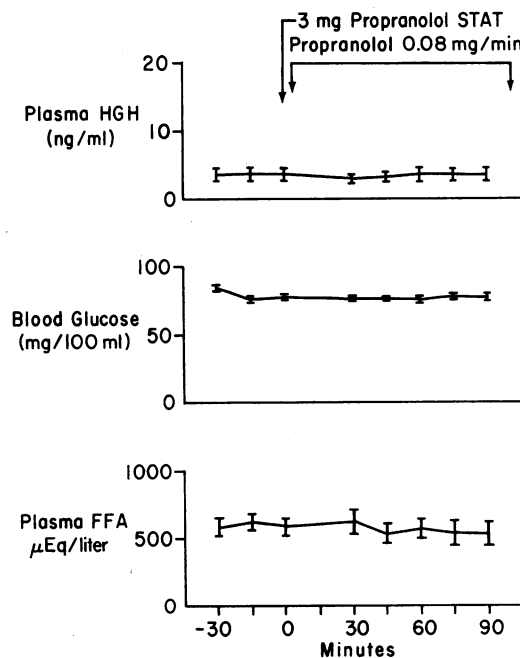


FIGURE 10 Effect of beta adrenergic blockade with propranolol on plasma HGH, blood glucose, and plasma FFA in seven normal subjects. Means \pm SEM are shown.

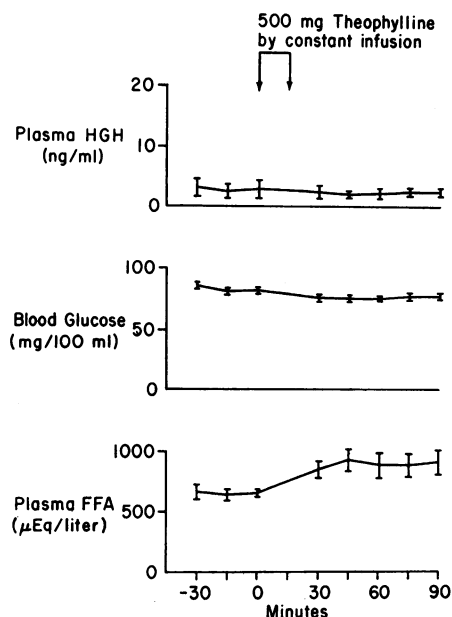


FIGURE 11 Effect of theophylline on plasma GHG, blood glucose, and plasma FFA in four normal subjects. Means \pm SEM are shown.

10). These results contrast with the greater suppressive effect of propranolol on catecholamine-induced FFA elevations such as occur during the "rebound" phase after insulin hypoglycemia (Fig. 6). In the later case, propranolol lowers plasma FFA by blocking the lipolytic action of catecholamines. However, in the absence of increased circulating catecholamines, phentolamine might have a greater suppressive effect on plasma FFA than propranolol through changes in insulin secretion (20).

Effect of theophylline on plasma GHG, blood glucose, and plasma FFA. Theophylline was given by infusion (500 mg in 15 min) to five subjects to determine the influence of inhibition of cyclic 3'5'-AMP phosphodiesterase activity on plasma GHG concentrations. No detectable effect on plasma GHG levels was observed, despite an increase in plasma FFA concentrations after theophylline infusion (Fig. 11).

DISCUSSION

The effect of catecholamines on growth hormone secretion has been controversial (2, 6, 13-16). In the present study, partial inhibition of the growth hormone response to hypoglycemia by alpha adrenergic blockade with phentolamine would tend

to indicate a stimulatory effect of catecholamines on growth hormone secretion. In previous investigations showing no effect (6, 15) or even some inhibition (2, 16) of growth hormone concentrations in response to epinephrine, catecholamine-induced hyperglycemia may have suppressed growth hormone secretion. By utilizing endogenous catecholamines released as a result of hypoglycemia for the blocking experiments in this investigation, we avoided the possible masking effect of hyperglycemia on plasma GHG concentrations.

The influence of catecholamines on growth hormone secretion might be exerted anywhere along the hypothalamic-hypophyseal axis and even perhaps at higher centers, but the hypothalamus seems the most likely site. Although the effect of hypoglycemia on growth hormone secretion may be only partially mediated by catecholamines, present evidence suggests that hypoglycemia initiates a growth hormone response by stimulating a discharge of growth hormone-releasing factor (GHRF) from the hypothalamus. Hypoglycemia depresses GHRF content in the rat hypothalamus (11) and increases plasma GHRF in hypophysectomized rats (21). The hypothalamus is rich in adrenergic neurons (22) for which catecholamines are the neurohumoral transmitters and it is tempting to postulate that the neurons which detect depression of blood glucose and stimulate release of GHRF are adrenergic. Although there is no complete agreement as to the site of GHRF production, recent data suggest that the ventromedial nucleus of the hypothalamus is essential for growth hormone secretion (23). The fact that the ventromedial nucleus is one of the few catecholamine-poor areas of the hypothalamus (22) makes it unlikely that this nucleus is stimulated directly by adrenergic neurons. However, the adrenergic tone of other areas of the hypothalamus may influence the ventromedial nucleus if indeed this is the source of GHRF. As the blood brain barrier for catecholamines present in most areas of the brain does not exist in the hypothalamus (24), circulating catecholamines from the adrenal medulla and other peripheral sources may be at least partly responsible for the growth hormone response during hypoglycemia.

It can not be concluded from the present experiments that the effect of hypoglycemia on growth hormone secretion is entirely mediated by

catecholamines since complete inhibition of HGH response could not be achieved with phentolamine. The growth hormone secretory mechanism is apparently sensitive to changes in blood glucose and not just to catecholamines released by hypoglycemia since elevations of blood glucose suppress HGH secretion (1). Catecholamines may merely modify the stimulatory effect of hypoglycemia on HGH release. Investigations by Sutin have shown an effect of insulin hypoglycemia on the evoked electrical potential recorded from a probe in the ventromedial nucleus of the hypothalamus after stimulation of the amygdala and septal nuclei (25). These changes in electrical potential from the ventromedial nucleus could be reproduced by injection of norepinephrine into the nucleus (26). Norepinephrine modified the amplitude of electrical response in the ventromedial nucleus to stimuli from other nuclei but did not initiate a response.

The stimulatory effect of catecholamines on growth hormone secretion has important implications as practically all of the recognized stimuli for growth hormone secretion, with the exception of amino acid infusion and estrogens, invoke a catecholamine response. Even small decreases in blood glucose (less than 10 mg/100 ml) which have been reported to elevate plasma HGH are accompanied by increased urinary catecholamines (6). In addition, the sympathetic tone in the hypothalamus may be important in the secretory regulation of other pituitary hormones. Hypothalamic catecholamine-depleting agents such as reserpine have been shown to influence gonadotropin secretion (27) as well as to inhibit the growth hormone response to hypoglycemia (28). Vasopressin secretion also is probably modified by adrenergic tone in the hypothalamus (29).

The present study characterized the growth hormone response to catecholamines in terms of alpha and beta adrenergic receptors. During insulin hypoglycemia the inhibitory effect of alpha blockade on growth hormone secretion was pronounced while the stimulatory effect of beta blockade was less impressive and was associated with more prolonged hypoglycemia and lower plasma FFA concentrations. More prolonged hypoglycemia probably was not responsible for the enhanced HGH response during beta blockade as studies in monkeys during insulin hypoglycemia have shown that growth hormone hypersecretion

occurs while blood glucose concentrations are falling but return to normal even though plasma glucose concentrations remain depressed (30). Limited data on the effect of plasma FFA on growth hormone levels are available. Schalch and Kipnis were unable to demonstrate an effect of plasma FFA elevations on plasma HGH concentrations in three subjects given a fat meal followed by heparin (31). However, preliminary data from Dr. K. Shizume in Tokyo (personal communication) have suggested that elevations of plasma growth hormone concentrations by nicotinic acid may be related to the fall in plasma FFA. Data by Abramson, Arky, and Woeber, which showed a modest increase in hypoglycemia-induced plasma HGH elevations during beta adrenergic blockade, support our findings (32).

The present studies demonstrate a definite stimulatory effect of alpha adrenergic receptors and a possible inhibitory effect of beta adrenergic receptors on growth hormone secretion. This pattern is the opposite of the adrenergic control mechanism for insulin secretion where it has been shown that alpha receptors inhibit (33) and beta receptors stimulate (34) insulin release. Since the predominant effect of catecholamines on hormonal regulation appear to be through alpha receptors, another remarkable homeostatic mechanism to maintain the constancy of the internal milieu is observed. During hypoglycemia, catecholamines inhibit insulin secretion and assist in promoting a rise in plasma HGH which antagonizes the action of insulin and also increases plasma FFA which may be used for energy requirements.

The lack of effect of adrenergic blockade or theophylline, an inhibitor of cyclic 3'5'-AMP phosphodiesterase activity, on plasma HGH concentrations in the absence of hypoglycemia probably negates a significant role of the adrenergic nervous system in control of resting plasma HGH levels.

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