JCI The Journal of Clinical Investigation

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J Clin Invest. 1971;50(5):1069-1079. https://doi.org/10.1172/JCI106578.

Research Article

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Effect of Adrenergic-Blocking or -Stimulating Agents on Plasma Growth Hormone, Immunoreactive Insulin, and Blood Free Fatty Acid Levels in Man

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ABSTRACT In order to determine whether an adrenergic mechanism is involved in the secretion of growth hormone and insulin, the effect of adrenergic-blocking or -stimulating agents on plasma human growth hormone (HGH), immunoreactive insulin, blood free fatty acids (FFA), and glucose levels was studied in normal human subjects.

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The intravenous infusion of alpha adrenergic–stimulating agents, phenylephrine and methoxamine, caused an increase in plasma HGH, a slight decrease in blood FFA, and no significant change in plasma insulin. This increase in plasma HGH was significantly inhibited by the simultaneous administration of phentolamine along with methoxamine. On the contrary, a beta adrenergic stimulant, isoproterenol, raised plasma insulin and blood FFA, and abolished the plasma HGH response to propranolol. Another beta stimulator, isoxsuprine, raised blood FFA but not plasma insulin.

It is concluded that either beta adrenergic blockade or alpha stimulation enhances HGH secretion and inhibits insulin secretion and fat mobilization, whereas either alpha blockade or beta stimulation stimulates insulin secretion and fat mobilization and inhibits HGH secretion.

INTRODUCTION

It has been clarified in recent years that secretion of human growth hormone (HGH)[1] is influenced by several factors, such as rapid changes in blood glucose level, amino acid ingestion, exercise, and stress (1–3). These stimuli appear to act through the hypothalamus, although the exact mechanism is still unknown. Several investigators (4–6) have demonstrated evidence for the presence of growth hormone–releasing factor (GRF), which is produced in the hypothalamus, transported to the anterior pituitary via the portal vessels, and stimulates HGH secretion. However, the chemical structure and the mechanism of secretion of GRF remain obscure. Since chemical transmitters such as norepinephrine, dopamine, acetylcholine are abundant in the hypothalamus, it is possible that these agents play an important role in regulating GRF secretion.

We have observed that resting levels of plasma HGH tended to be elevated in patients with pheochromocytoma, with a tendency to an exaggerated response to insulin-

This work was presented at the Third International Congress of Endocrinology, Mexico City, Mexico, July 1968. A portion of this study was published as a preliminary communication in 1968. *J. Clin. Endocrinol. Metab.* **28**: 1079.

Received for publication 21 July 1970 and in revised form 4 January 1971.

[1] *Abbreviations used in this paper:* FFA, free fatty acids; GRF, growth hormone-releasing factor; HGH, human growth hormone; IRI, immunoreactive insulin.

induced hypoglycemia and the lack of a normal response to oral glucose administration (7). These abnormalities suggest that catecholamines may play a role in regulating HGH secretion. Although it has been reported that the injection of catecholamines did not influence plasma HGH levels in man (1, 8, 9), we thought it interesting to study further the role of the adrenergic mechanisms in regulating HGH secretion.

These studies are also interesting in another aspect. Porte, Graber, Kuzuya, and Williams (10) and Porte (11) have reported that the adrenergic mechanism is involved in insulin secretion and that beta adrenergic receptor blockade suppresses insulin secretion, whereas alpha blockade stimulates it. Since there are close relationships between insulin and HGH secretion, it seemed worthwhile to compare the adrenergic receptor mechanisms for the secretion of these two hormones.

In the present experiments, the effect of adrenergic-blocking or -stimulating agents on plasma HGH and IRI levels were studied in normal subjects. It was demonstrated that either beta adrenergic blockade or alpha stimulation enhanced HGH secretion and suppressed insulin secretion, whereas either alpha blockade or beta stimulation enhanced insulin secretion and suppressed HGH secretion.

METHODS

Male and female volunteers, aged 19–42, were used throughout the experiments. None of them had a family history of diabetes nor elevated fasting blood sugar level. They were nonobese (less than 15% above ideal body weight) and apparently normal in endocrine and autonomic nervous function. Some subjects were used for several experiments with an interval of at least 1 wk between the two experiments, whereas others were used for only one experiment.

The subjects were not allowed to smoke or to take anything by mouth except water after 10 p.m. the night before the study. They came to the laboratory at 8:00–8:30 a.m. and then lay still throughout the experiment. Two control blood specimens were withdrawn between 9:00 and 9:30 a.m., and a slow intravenous infusion of 500 ml of physiologic saline containing adrenergic-blocking or -stimulating agents was given at a constant rate over a period of 2 hr through a 20 gauge needle into the antecubital vein. Blood was withdrawn from the opposite antecubital vein every 15 or 30 min until 1 hr after the end of the infusion. Repeated venopuncture was usually performed for drawing blood with a 21 gauge needle and a heparinized syringe. An aliquot of blood was used for the determination of blood glucose and free fatty acids (FFA) levels. The remaining portion was centrifuged as soon as possible. Plasma was separated, frozen, and stored for the measurement of plasma immunoreactive insulin (IRI) and HGH.

Blood glucose was measured by a ferricyanide reduction method with a Technicon AutoAnalyzer (Technicon Co., Inc., Tarrytown, N. Y.). Blood FFA concentration was determined by a modification of the colorimetric method of Itaya and Ui (12). In this modified method, hydroxylamine hydrochloride, acetic acid, and batho-cuproine[2] were used instead of sodium diethyldithiocarbamate to develop the color of the copper salts of fatty acids extracted in chloroform because this modification gives better reproducibility. Plasma IRI was measured by the immunoassay kit of the Radiochemical Centre (Amersham, England) which is based upon the double antibody immunoprecipitation technique (method C) of Hales and Randle (13). The minimal detectable quantity of IRI for the assay was 5 μU/ml. Repeated determinations of two pooled plasmas on 10 different days gave coefficients of variance of 8.8% and 10.1%, for the two pools.

Plasma HGH was measured by the double antibody radioimmunoassay of Schalch and Parker (14). Anti-HGH serum was prepared in a guinea pig by several weekly injections of 1 mg of HGH (Li) emulsified in 0.5 ml of complete Freund's adjuvant. This antiserum showed one precipitation arc with HGH, but not with human serum when tested by immunoelectrophoresis. Anti-guinea pig γ-globulin serum was obtained from rabbits which received repeated injections of guinea pig γ-globulin in complete Freund's adjuvant. HGH (Wilhelmi, HS705A) was labeled with ^{131}I by the method of Greenwood, Hunter, and Glover (15). Specific activities of 150–450 μCi/μg were obtained. All standards (Wilhelmi's HGH) and plasma samples were assayed in duplicate. The minimal detectable value of HGH for the assay was 0.1 mμg/ml. In plasma assays at various levels, the range of difference between duplicates as millimicrograms per milliliter was usually less than 10%.

In order to determine the effect of beta adrenergic blockade, intravenous infusions of 10 mg of propranolol were given to 14 subjects (7 males and 7 females). Concomitant administration of 10 mg of propranolol with 0.36 mg of isoproterenol or with 0.72 mg of epinephrine was performed in four and five subjects, respectively. In five subjects, 50 g of glucose was given orally immediately before the start of propranolol infusion, to determine whether glucose administration influences the HGH response to propranolol.

In the second series of experiments, the effect of an alpha adrenergic-blocking agent on plasma HGH and IRI was studied. Either 10 mg or 20 mg of phentolamine dissolved in 500 ml of saline was infused in six normal subjects. In another six subjects, intravenous infusions of 20 mg of phentolamine in 500 ml saline and 30 g of l-arginine in 500 ml solution were started at the same time in both antecubital veins and continued for 2 hr and 30 min, respectively. 1 wk later, 500 ml of physiologic saline and l-arginine solution were infused in the same normal subjects as a control experiment. In another three subjects, 20 mg of phentolamine was infused over a period of 2 hr. Immediately after the start of infusion, glucagon-free insulin (0.1 U/kg body weight) was injected intravenously. After 1 wk, insulin was given during the infusion of 60 mg of phentolamine in the same subjects, and 1 wk later, insulin was injected during the infusion of physiologic saline as a control experiment.

[2] *Trivial names used in this paper:* propranolol, 1-isopropylamino)-3-(1-naphthyloxy)-2-propanol; isoproterenol, 3,4-dihydroxy-α-[(isopropylamino)methyl]-benzyl alcohol; phentolamine, 2-[*N*-(*m*-hydroxyphenyl)-*p*-toluidinomethyl] imidazoline; phenylephrine, 1-*m*-hydroxy-α-[(methyl-amino) methyl] benzyl alcohol hydrochloride; methoxamine, α-(1-aminomethyl)-2,5-dimethoxybenzyl alcohol hydrochloride; isoxsuprine, *p*-hydroxy-α-{1-[(1-methyl-2-phenoxyethyl)-amino] ethyl} benzyl alcohol; batho-cuproine, 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline.

TABLE I

Effect of Intravenous Infusion of 10 mg of Propranolol on Plasma HGH and Blood FFA Levels in Normal Subjects

Subjects	Age	Sex	Time (minutes) 0	15	30	60	90	120	135	150	180	0	15	30	60	90	120	135	150	180
			Plasma HGH (*mμg/ml*)									Blood FFA (*μEq/liter*)								
H. I.	19	F	2.4	1.0	1.6	8.2	17.6	8.0	3.2	5.6	10.8	456	366	264	228	348	418	420	304	414
T. M.	36	F	11.6	9.4	12.4	18.4	14.4	19.2	14.4	19.6	15.2	570	434	402	348	418	594	598	521	690
S. U.	42	F	7.8	9.2	10.6	24.0	17.2	9.6	10.4	11.2	9.0	488	484	379	370	320	325	341	357	440
M. I.	23	F	10.6	10.8	10.4	9.6	15.0	20.4	15.8	11.2	10.6	308	273	238	160	155	144	263	363	440
S. W.	20	F	4.6	20.0	34.4	15.2	15.2	10.9	15.7	16.0	4.7	376	174	210	254	235	347	310	281	263
Y. M.	20	F	5.3	10.0	20.9	20.6	6.6	4.4	3.4	3.9	5.2	—	—	—	—	—	—	—	—	—
H. S.	20	F	1.9	0.8	1.2	7.2	6.5	0.8	0.7	0.5	0.4	—	—	—	—	—	—	—	—	—
T. Y.	42	M	2.9	3.4	14.4	32.4	27.6	13.6	9.9	8.4	4.2	413	372	320	330	421	414	304	397	468
R. S.	36	M	3.5	3.2	16.0	28.8	7.2	3.8	4.4	5.6	6.8	422	334	327	312	443	490	540	348	370
S. I.	23	M	3.5	2.8	2.7	5.4	11.4	18.0	9.4	6.2	11.4	424	372	440	450	406	469	421	233	199
K. F.	25	M	3.7	3.8	4.9	4.6	6.3	4.3	5.0	5.3	3.9	242	336	270	204	371	339	261	228	150
G. Y.	22	M	3.3	3.1	3.4	3.4	25.2	39.8	22.8	11.3	8.1	283	309	360	170	231	291	180	353	120
K. M.	24	M	6.2	6.2	6.2	16.2	7.6	7.0	7.8	6.6	7.6	596	531	382	348	489	496	645	640	530
N. K.	21	M	2.6	1.8	1.8	2.5	2.4	3.2	—	1.8	4.2	234	278	452	350	399	302	—	238	308
	Mean		5.0	6.1	10.1	14.1	12.7	11.6	9.5	8.1	7.5	441	355	337	294	333	386	357	355	373
	SEM		0.8	1.4	2.6	2.6	2.0	2.7	1.8	1.4	1.0	30	24	18	22	25	29	36	30	40
			Plasma IRI (*μU/ml*)									Blood sugar (*mg/dl*)								
	Mean		7.5	7.6	4.6	5.3	5.5	5.4	6.9	9.2	9.0	75	74	74	72	73	72	77	73	69
	SEM		2.5	2.5	1.5	1.5	1.8	1.8	2.3	3.1	3.0	3	3	3	3	3	2	3	3	3

Intravenous infusion of an alpha adrenergic-stimulating agent, 1 mg, 3 mg, or 10 mg of phenylephrine, in 500 ml of saline solution was performed over a period of 2 hr in 10 subjects. Another alpha-stimulating agent, 25 mg of methoxamine, was infused in seven subjects. Combined administation of 25 mg of methoxamine and 20 mg of phentolamine in 500 ml of saline was performed in four subjects. Intravenous infusions of two different beta adrenergic-stimulating agents, 15 mg or 30 mg of isoxsuprine and 0.36 mg of isoproterenol, were given to six and four subjects, respectively. As a control, 500 ml of physiologic saline was given intravenously over a period of 2 hr in six normal subjects.

Propranolol (Inderal) was kindly supplied by Sumitomo Chemical Industry Co., Osaka, Japan. Phentolamine (Regitine) was purchased from Ciba Products Co., Osaka, Japan. Phenylephrine (Neo Synesin) and methoxamine (Vasoxyl) were gifts from Kowa Co., Nagoya, Japan, and Burroughs Wellcome Co. Inc., Tuckahen, N. Y., respectively. Isoxsuprine (Duvadilan) was supplied by Dai-ichi Seiyaku Co., Tokyo, Japan. Isoproterenol (Proternol-L) was purchased from Nikken Kagaku Co., Tokyo, Japan. Arginine solution was kindly supplied by Tanabe Pharmaceutical Co., Osaka, Japan.

RESULTS

Effect of beta adrenergic-blocking agent on plasma HGH, IRI, blood FFA, and glucose. Table I summarizes the effect of intravenous infusion of propranolol on plasma HGH and IRI, blood FFA, and glucose levels. Plasma HGH rose significantly during the infusion of propranolol in 13 of 14 subjects and reached a peak 30–120 min after the start of the propranolol infusion. Mean plasma HGH level 60 min after the start of the infusion was 14.1 mμg/ml with the standard error of 2.61 mμg/ml. The peak plasma HGH levels in the 13 cases were from 6.3 to 39.8 mμg/ml, with the mean value of 21.9 mμg/ml. No significant sex difference was observed in the plasma HGH response to propranolol. Blood FFA exhibited a transient decrease with the minimum mean level at 60 min of the infusion and then returned to the basal levels in 11 of 12 subjects tested. Case 14 who failed to exhibit an HGH response to propranolol showed a rise in blood FFA during the infusion of propranolol. No significant difference was observed in blood sugar and plasma IRI in any of the subjects tested.

The concomitant administration of isoproterenol, a beta adrenergic-stimulating agent, with propranolol completely abolished plasma HGH response to propranolol in all subjects tested as shown in Fig. 1. The plasma IRI response to isoproterenol, described later in this paper, was also completely suppressed by the simultaneous infusion of propranolol. A transient rise in blood FFA was observed, whereas no significant change was noted in blood glucose throughout the experiment.

Combined intravenous infusion of epinephrine with propranolol brought about almost the same rise in plasma HGH as did propranolol alone as shown in Fig. 2. Peak plasma HGH levels during the combined infusion were from 8.4 to 35.9 mμg/ml. Blood FFA concentrations did not change significantly until 90 min after the start of the infusion and then declined gradually. Blood glucose rose significantly to a peak 90 min after the start of the infusion. Plasma IRI rose slightly only after the end of the infusion, in spite of the significant increase in blood glucose levels during the infusion.

The oral administration of 50 g of glucose given immediately before the start of the propranolol infusion

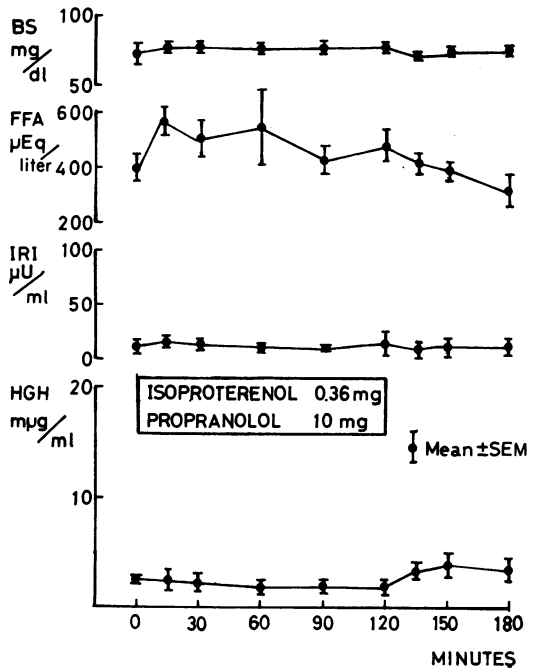

FIGURE 1 Effect of concomitant administration of propranolol and isoproterenol on plasma HGH, IRI, blood FFA, and glucose (BS) in four normal subjects. Both 10 mg of propranolol and 0.36 mg of isoproterenol were dissolved in 500 ml of saline solution and infused over a period of 2 hr. Means ±SEM are shown.

completely suppressed plasma HGH response to propranolol as shown in Fig. 3, although a slight but significant rise in plasma HGH was observed in three of five subjects 150–180 min after the start of the infusion. Plasma IRI response to the oral administration of glucose was significantly lower during the infusion of propranolol (mean peak level was 21.0 μU/ml with the standard error of 4.59 μU/ml), since the mean peak IRI value after oral glucose was 78.2 μU/ml with the standard error of 10.2 μU/ml in 14 normal subjects without infusion of propranolol ($P < 0.01$, in paired t test). Although the plasma IRI response to glucose was thus significantly suppressed during the infusion of propranolol, blood glucose curves were not significantly different from those obtained without the infusion of propranolol. Blood FFA levels were decreased gradually through the experiment when propranolol infusion was performed, whereas rebound of blood FFA was observed 180 min after the oral glucose loading without the infusion of propranolol.

Effect of alpha adrenergic-blocking agent on plasma HGH, IRI, blood FFA, and glucose. Intravenous infusion of phenotolamine caused a slight decline in plasma HGH, a slight increase in plasma IRI, a significant increase in blood FFA, and no significant change in blood glucose as shown in Fig. 4. There were no significant differences in plasma HGH, IRI, blood FFA, and glucose between the two groups given 10 mg and 20 mg of phentolamine, respectively.

The plasma HGH response to the intravenous infusion of arginine was significantly lower during the infusion of phentolamine than in control experiments ($P < 0.02$), as shown in Figs. 5 and 6. On the other hand, the plasma IRI response to arginine infusion was significantly higher during the infusion of phentolamine than in control experiments ($P < 0.05$). There was no significant difference in blood glucose and FFA responses to arginine infusion.

The plasma HGH response to insulin-induced hypoglycemia was significantly suppressed during the infusion of phentolamine as shown in Table II. The peak HGH values after insulin injection were much lower in subjects given 60 mg of phentolamine than in those given 20 mg.

Effect of alpha adrenergic-stimulating agents on plasma HGH, IRI, blood FFA, and glucose. The intravenous infusion of 1 or 3 mg of phenylephrine, an

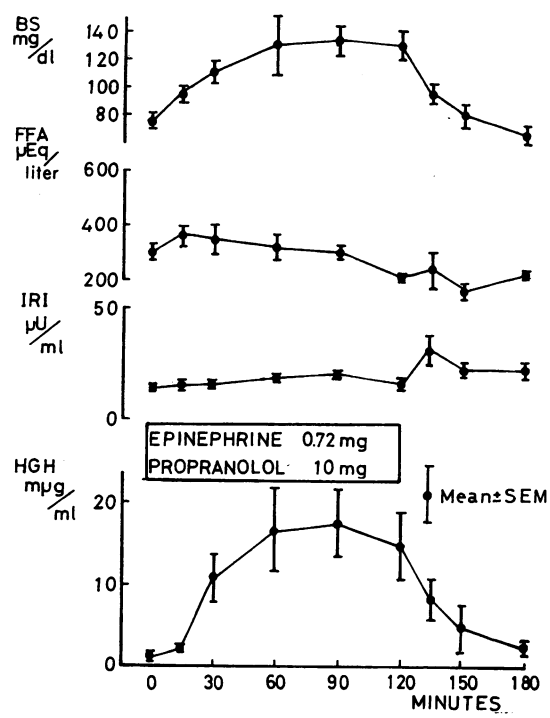

FIGURE 2 Effect of concomitant administration of propranolol and epinephrine on plasma HGH, IRI, blood FFA, and glucose (BS) in five normal subjects. Both 10 mg of propranolol and 0.72 mg of epinephrine were dissolved in 500 ml of saline solution and infused over a period of 2 hr. Means ±SEM are shown.

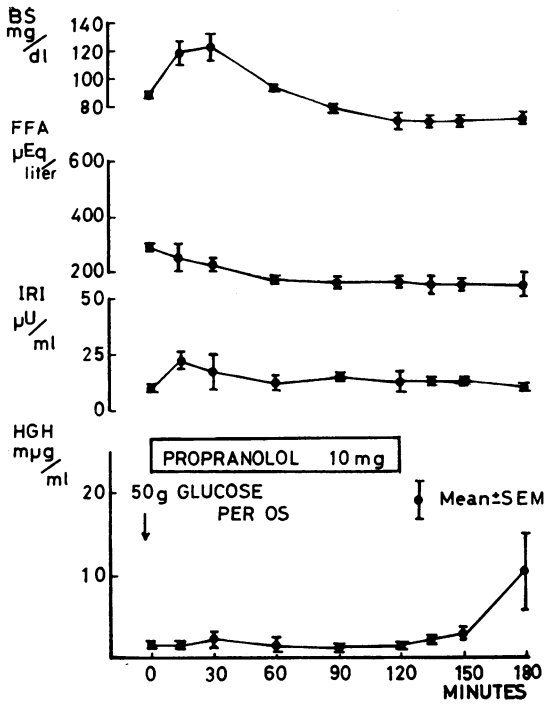

FIGURE 3 Effect of glucose administration on plasma HGH, IRI, and blood FFA responses to propranolol infusion in five normal subjects. Immediately before the start of the propranolol infusion, 50 g of glucose was given orally. Means ±SEM are shown.

alpha adrenergic–stimulating agent, caused a significant increase in plasma HGH during the infusion in two and after the end of the infusion in three of seven subjects tested (Table III). There seemed to be no significant difference in plasma HGH response between three subjects given 1 mg and four subjects given 3 mg of phenylephrine. However, no significant change in plasma HGH was noted in subjects given 10 mg of phenylephrine (Table III). Blood FFA concentrations were transiently decreased during the infusion of 1 mg of phenylephrine, but increased during the infusion of 10 mg of the drug as shown in Table III. No significant change was observed in blood glucose and plasma IRI in all the subjects tested.

Intravenous infusion of another alpha adrenergic–stimulating agent, methoxamine, caused a rise in plasma HGH during the infusion in all subjects tested as shown in Fig. 7. A transient, slight decline in blood FFA concentrations was observed during the infusion, whereas no significant change was noted in blood glucose.

Plasma HGH response to methoxamine was significantly blunted by the simultaneous administration of phentolamine, an alpha adrenergic–blocking agent, as shown in Fig. 8 ($P < 0.05$). The increase in plasma IRI caused by phentolamine was also suppressed by the combined administration of methoxamine. Blood FFA rose slightly during the combined administration, whereas it tended to decrease during the infusion of methoxamine alone.

Effect of beta adrenergic–stimulating agents on plasma HGH, IRI, blood FFA, and glucose. Plasma HGH levels tended to decrease during the infusion of isoxsuprine, a beta adrenergic–stimulating agent, although they increased slightly in four of six subjects after the end of infusion as shown in Fig. 9. Blood FFA concentrations rose significantly during the infusion, whereas plasma IRI and blood glucose were not significantly changed.

The intravenous infusion of isoproterenol, another beta adrenergic–stimulating agent, caused a significant rise in plasma IRI and blood FFA and no significant change in plasma HGH and blood glucose as shown in Fig. 10.

Effect of saline infusion on plasma HGH, IRI, blood FFA, and glucose. Plasma HGH levels tended to decrease in three and were almost unchanged in two of five subjects during the infusion of saline solution. No consistent change was noted in plasma IRI, blood FFA, and glucose as shown in Fig. 11.

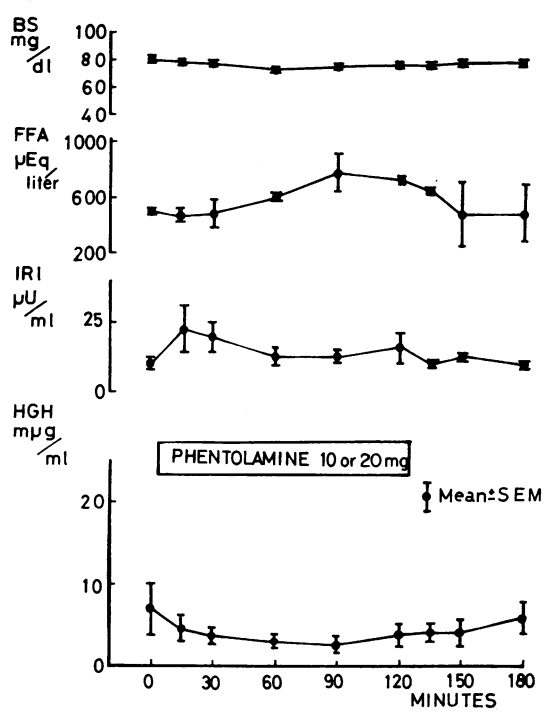

FIGURE 4 Effect of intravenous infusion of 10 or 20 mg of phentolamine on plasma HGH, IRI, blood FFA, and glucose (BS) levels in five normal subjects. Since there were no significant differences between two groups given 10 mg and 20 mg of the drug, all data were pooled and shown as means ±SEM.

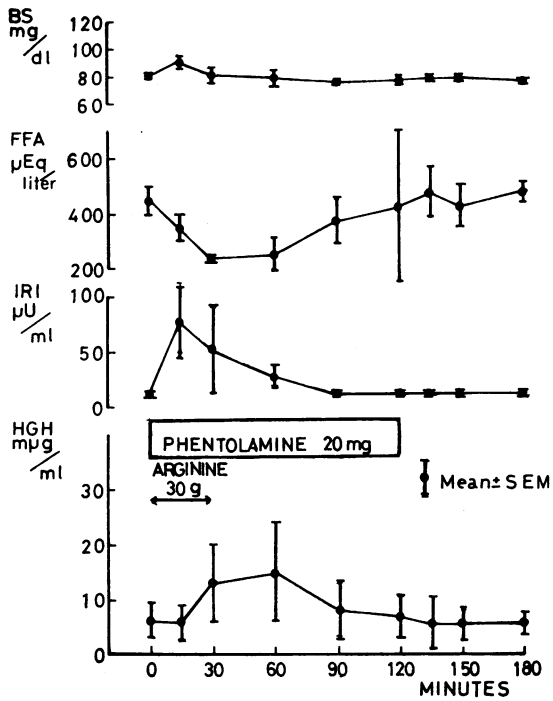

FIGURE 5 Plasma HGH, IRI, blood FFA, and glucose (BS) responses to arginine during the infusion of phentolamine in six normal subjects. Intravenous infusion of l-arginine (30 g in 500 ml) and phentolamine (20 mg in 500 ml saline solution) were started at the same time. The former continued for 30 min and the latter for 2 hr. Means ±SEM are shown.

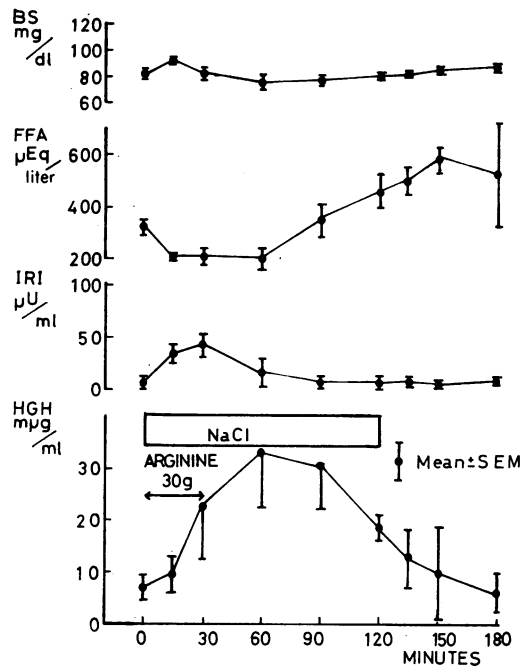

FIGURE 6 Plasma HGH, IRI, blood FFA, and glucose (BS) responses to arginine during the infusion of saline in six normal subjects. Intravenous infusions of l-arginine (30 g in 500 ml) and 500 ml of saline were started at the same time and continued for 30 min and 2 hr, respectively. Means ±SEM are shown.

TABLE II

*Mean Plasma HGH, Blood FFA, and Glucose Responses to Insulin during the Infusion of Saline or Phentolamine**

	Time (minutes)								
	0	15	30	60	90	120	135	150	180
Blood glucose (*mg/dl*)									
Saline	81.3	40.0	28.7	52.7	66.7	74.7	78.0	84.0	89.3
Phentolamine									
20 mg	87.3	42.3	30.0	54.7	70.7	74.7	88.7	84.7	86.7
60 mg	93.3	76.0	42.0	72.0	87.3	98.0	88.0	90.0	97.3
Blood FFA (*μEq/liter*)									
Saline	389.7	280.7	238.0	368.7	402.3	426.0	468.7	482.7	549.3
Phentolamine									
20 mg	264.0	152.3	309.7	335.0	331.3	417.7	454.0	402.3	462.0
60 mg	383.7	297.0	303.7	413.3	398.3	395.7	395.3	395.7	393.3
Plasma HGH (*mμg/ml*)									
Saline	1.9	1.9	6.3	36.2	33.5	21.3	24.0	9.7	8.2
Phentolamine									
20 mg	3.1	3.0	4.8	24.4	24.0	14.2	—	8.4	5.6
60 mg	1.7	1.7	1.7	7.8	4.8	4.4	2.8	2.4	1.1

* Glucagon-free insulin (0.1 U/kg body weight) was injected intravenously immediately after the start of saline (500 ml) or phentolamine (20 or 60 mg in 500 ml saline) infusion. Means obtained in three subjects are shown.

TABLE III

Effect of Intravenous Infusion of 1, 3, or 10 mg of Phenylephrine on Plasma HGH and Blood FFA in Normal Subjects

Subjects	Age	Sex	Plasma HGH (mμg/ml) 0	15	30	60	90	120	135	150	180	Blood FFA (μEq/liter) 0	15	30	60	90	120	135	150	180
Time (minutes)...																				
	yr																			
Phenylephrine, 1 mg																				
D. S.	24	M	10.9	34.4	45.6	40.0	14.0	5.3	3.0	2.0	1.9	336	201	204	284	405	428	372	314	504
M. K.	23	M	0.4	0.4	0.4	0.4	0.5	0.5	0.3	0.6	1.1	359	381	390	357	351	251	264	318	219
T. N.	21	M	1.2	2.0	1.5	1.1	1.0	1.4	1.0	11.2	28.0	225	282	175	167	158	232	201	258	217
Mean			4.1	12.3	15.8	13.8	5.2	2.3	1.4	4.6	10.3	306	288	230	269	305	303	279	297	280
Phenylephrine, 3 mg																				
Y. N.	22	M	1.5	1.2	1.7	3.9	1.5	1.8	2.0	10.0	16.0	—	—	—	—	—	—	—	—	—
T. A.	20	M	2.6	6.0	6.9	16.0	4.4	4.2	1.3	1.9	2.4	374	302	308	327	288	300	410	233	300
M. T.	20	M	2.1	2.0	1.2	1.6	2.7	2.0	2.2	1.6	2.5	198	132	190	182	232	205	199	199	126
Y. M.	19	F	3.6	2.1	3.0	2.5	2.1	2.8	8.6	11.8	14.0	265	247	419	361	393	397	413	265	257
Mean			2.4	2.8	4.2	8.0	2.7	2.9	3.5	6.3	8.7	279	227	306	290	304	301	341	232	228
Phenylephrine, 10 mg																				
T. M.	20	M	1.0	1.0	0.9	0.8	1.1	1.0	0.9	1.5	1.2	240	117	178	245	295	285	193	158	108
N. Y.	22	M	1.9	2.0	1.2	0.9	1.2	2.5	2.1	1.2	1.2	163	304	308	302	476	373	396	432	278
Y. N.	22	M	0.8	1.0	0.8	1.1	0.9	1.5	1.3	1.2	1.0	502	453	636	676	649	537	547	342	380
Mean			1.2	1.3	1.0	1.0	1.1	1.7	1.4	1.3	1.1	302	291	374	408	473	398	378	310	255

DISCUSSION

The present studies demonstrate that the intravenous infusion of propranolol, a beta adrenergic–blocking agent, stimulates HGH secretion in almost all normal subjects of both sexes. This stimulating effect of propranolol was completely inhibited by the combined administration of a beta adrenergic–stimulating agent, isoproterenol. It suggests that propranolol stimulates HGH secretion through blockade of beta adrenergic receptors.

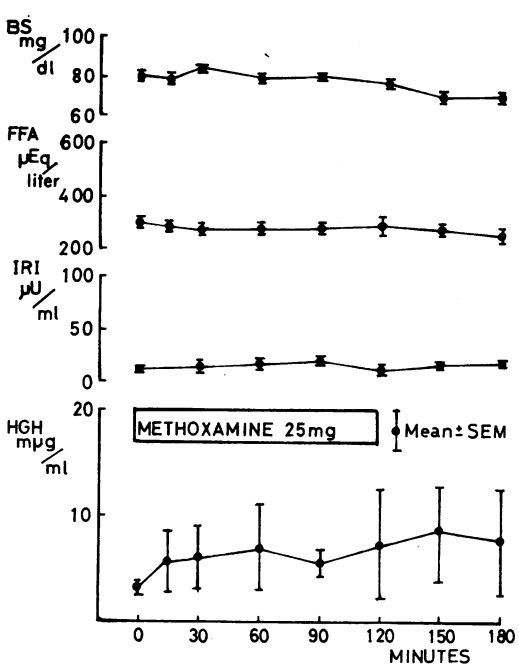

FIGURE 7 Effect of intravenous infusion of 25 mg of methoxamine on plasma HGH, IRI, blood FFA, and glucose (BS) in seven normal subjects. Means ±SEM are shown.

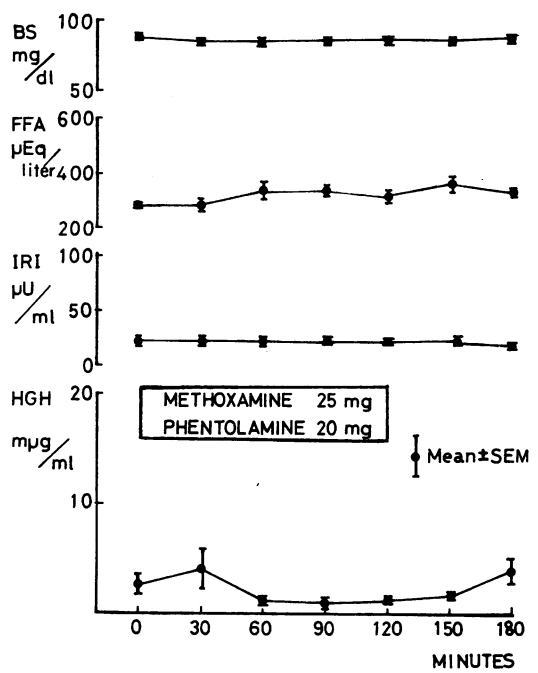

FIGURE 8 Effect of concomitant administration of methoxamine and phentolamine on plasma HGH, IRI, blood FFA, and glucose (BS) in four normal subjects. Both 25 mg of methoxamine and 20 mg of phentolamine were dissolved in 500 ml saline and infused over a period of 2 hr. Means ±SEM are shown.

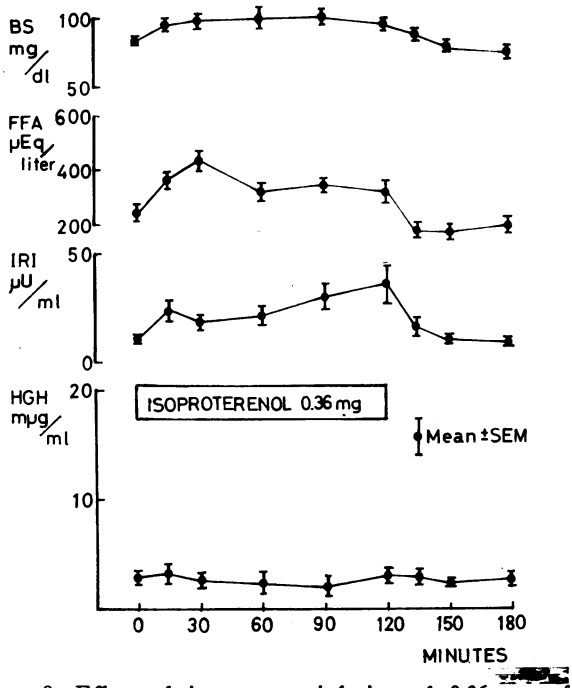

FIGURE 9 Effect of intravenous infusion of 0.36 mg of isoproterenol on plasma HGH, IRI, blood FFA, and glucose (BS) in four normal subjects. Means ±SEM are shown.

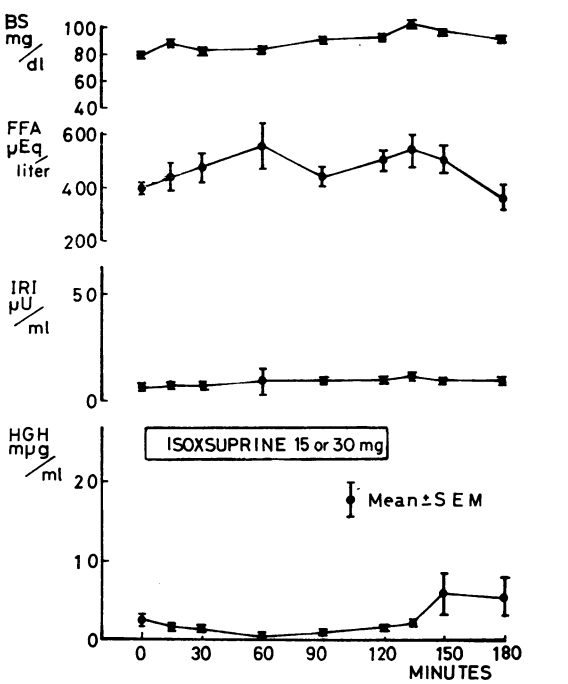

FIGURE 10 Effect of intravenous infusion of 15 or 30 mg of isoxsuprine on plasma HGH, IRI, blood FFA, and glucose (BS) in six normal subjects. Means ±SEM are shown.

It was also demonstrated that HGH secretion caused by propranolol is suppressed by the oral administration of glucose, like HGH secretion induced by hypoglycemia, exercise, and amino acid infusion (1, 16). The fact that the combined administration of propranolol and epinephrine caused a rise in plasma HGH in spite of an increase in blood glucose needs comment. This can be explained, however, by the time relationship between the increase of blood glucose and HGH secretion. Just as glucose given 45 min after the injection of insulin cannot prevent the rise in plasma HGH (1), so a blood glucose peak occurring 90 min after the start of the propranolol and epinephrine infusion would not affect HGH secretion elicited by propranolol.

The intravenous infusion of propranolol caused a transient decrease in blood FFA in almost all the subjects tested. Inasmuch as Irie, Sakuma, Tsushima, Shizume and Nakao (17) reported that a decrease in blood FFA may be a potent stimulus for HGH secretion, it is possible that the HGH secretion caused by propranolol is due to the effect of decreased blood FFA. This is unlikely, however, because the combined administration of epinephrine and propranolol produced a significant rise in plasma HGH without any significant change in blood FFA.

Blackard and Heidingsfelder (18) observed in their experiments independently performed from ours (19) that the intravenous administration of propranolol caused

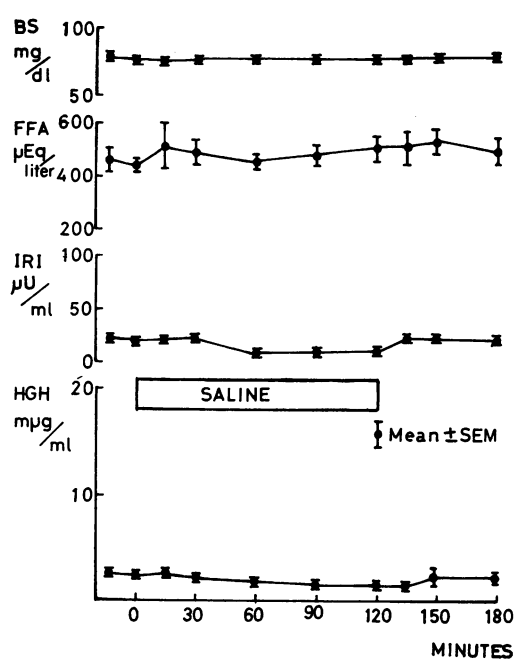

FIGURE 11 Effect of intravenous infusion of saline on plasma HGH, IRI, blood FFA, and glucose (BS) in six normal subjects. Means ±SEM are shown.

no significant change in plasma HGH, although it enhanced plasma HGH response to insulin-induced hypoglycemia. They reported also that blood FFA concentrations were not changed significantly by the administration of propranolol, whereas we observed a decrease in blood FFA. The total dose of the drug was the same in these two experiments, although the schedule of administration was different. Since the average body weight of the Japanese is much lower than that of Americans, the dosage of propranolol per kilogram of body weight was certainly greater in our experiment. Werbach, Gale, Goodner, and Conway (20) demonstrated an increase in plasma HGH during the infusion of propranolol in baboons, using the dose (per kilogram body weight) more than 3 times greater than that in our experiment.

The intravenous administration of phentolamine, an alpha adrenergic–blocking agent, caused a slight decrease in plasma HGH. This observation is not conclusive because a decrease in plasma HGH is often observed only during rest, especially when basal HGH levels are slightly elevated. We observed, however, that phentolamine partially but significantly blunted the plasma HGH responses to insulin-induced hypoglycemia and to arginine infusion. These results agree with the observation of Blackard and Heidingsfelder (18) that phentolamine partially inhibited plasma HGH response to insulin-induced hypoglycemia.

The present experiment also demonstrated that phentolamine significantly enhanced the plasma IRI response to arginine infusion. It has been known that epinephrine inhibits plasma IRI responses to glucose, glucagon, and tolbutamide (10) and that phentolamine stimulates IRI release when infused with epinephrine (11). However, the effect of epinephrine on insulin secretion elicited by amino acids is still controversial (8, 21, 22), and the effect of adrenergic-blocking agents on amino acid–induced insulin release is unknown. The present experiment strongly suggests that alpha adrenergic blockade enhances the insulin secretion elicited by amino acids.

The effect of adrenergic-stimulating agents on plasma HGH and IRI was less clear-cut than that of adrenergic-blocking agents, probably because adrenergic-stimulating agents are usually less specific than blocking agents. For example, phenylephrine is a potent alpha receptor stimulant, but with a little stimulating effect on beta receptors (23). A small dose of phenylephrine brought about a rise in plasma HGH and a decrease in blood FFA in most of the subjects, although a large dose of the drug failed to increase plasma HGH and even raised blood FFA. These results suggest that alpha stimulation is predominant with a small dose of phenylephrine, whereas beta stimulation becomes apparent after a large dose, although the possibility of chance variation could not be ruled out completely because of a small number of the subjects tested.

TABLE IV

Effect of Adrenergic Blockade or Stimulation on Growth Hormone and Insulin Secretion and Fat Mobilization

	HGH secretion	Insulin secretion	Fat mobilization*
Alpha blockade	Suppressed	Enhanced	Enhanced
Alpha stimulation	Enhanced	Suppressed	Suppressed
Beta blockade	Enhanced	Suppressed	Suppressed
Beta stimulation	Suppressed	Enhanced	Enhanced

* Although fat mobilization was not measured directly, changes in blood FFA are assumed to reflect comparable changes in fat mobilization in the present experiment.

Another alpha-stimulating agent, methoxamine, which is known to stimulate alpha receptors almost exclusively, enhanced HGH secretion more markedly than did phenylephrine. This increase in plasma HGH caused by methoxamine was significantly blunted by the simultaneous administration of phentolamine, an alpha-blocking agent. These results suggest that alpha receptors enhance HGH secretion.

A beta adrenergic–stimulating agent, isoproterenol, raised plasma IRI and blood FFA, as already demonstrated by Porte (24). It completely abolished plasma HGH response to propranolol. Another beta-stimulating agent, isoxsuprine, failed to raise plasma IRI, whereas it increased blood FFA significantly. This discrepancy may be explained either by differences in relative dosage or by different properties of these two drugs. Isoproterenol acts almost exclusively on beta receptors, whereas isoxsuprine is known to have some effect on alpha receptors also (25). Further studies on the effect of beta stimulants on plasma HGH responses to insulin-induced hypoglycemia or to arginine are required to establish the inhibitory effect of beta stimulants on HGH secretion.

Table IV summarizes the results of the present experiment. Beta adrenergic blockade stimulates HGH secretion and inhibits insulin secretion and fat mobilization. Alpha adrenergic stimulation similarly stimulates HGH secretion and inhibits insulin secretion and fat mobilization. On the contrary, either alpha adrenergic blockade or beta stimulation inhibits HGH secretion and enhances both insulin secretion and fat mobilization. The fact that the administration of catecholamines failed to stimulate HGH secretion (1, 8, 9) may be explained by the simultaneous stimulations of beta receptors which inhibit HGH secretion.

It is noteworthy that the adrenergic receptor mechanisms for HGH and insulin secretion are opposite. HGH and insulin secretion are known to be regulated inversely by the change of blood glucose and FFA levels

(1, 17). A fall in blood glucose stimulates the secretion of catecholamines, which inhibit insulin secretion and probably assist in enhancing HGH secretion through alpha receptors. Although a single injection of catecholamines fails to affect HGH levels in man, we observed that consistent elevation of plasma catecholamines in pheochromocytoma enhances HGH secretion induced by hypoglycemia and prevents suppression of HGH secretion by glucose administration (7).

In vitro experiments on the effect of adrenergic agents on fat mobilization from adipose tissue and on insulin secretion from the islets of the pancreas indicate that the adrenergic mechanism may reside in the fat cells or in the islet cells themselves (26, 27). However, it is still unknown in what process the adrenergic mechanism may be involved in HGH secretion. It might reside anywhere in the hypothalamo-hypophyseal system or even in another portion of the central nervous system. However, the hypothalamus is the most likely site because of its high norepinephrine content as well as abundant adrenergic neurons and because of the fact that norepinephrine depletors block growth hormone release induced by hypoglycemia but not by GRF (28). It is possible, therefore, that the neurons which detect stimuli such as a fall in blood sugar and stimulate discharges of GRF are adrenergic. However, the possibility of dopaminergic neurons cannot be ruled out completely, since Schneider and McCann (29) reported that dopamine stimulates LH release from the pituitary when incubated with stalk median eminence tissue and that phentolamine inhibits the action of dopamine. It seems reasonable to speculate, therefore, that alpha adrenergic receptors stimulated by norepinephrine, or possibly dopamine, enhance GRF secretion.

ACKNOWLEDGMENTS

We are greatly indebted to Professor Masaichi Fukase for his valuable advice to this study. Thanks are also due to Professor C. H. Li and Professor A. E. Wilhelmi for the supply of human growth hormone.

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