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The Control on Growth Hormone Release by Free Fatty Acids Is Maintained in Acromegaly

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ABSTRACT

Free fatty acids (FFA) physiologically regulate GH release via a negative feedback. The aim of this study was to examine whether such feedback is preserved in acromegaly, a condition in which alterations in other regulatory mechanisms of GH release occur. Eight acromegalic patients (group 1: five women and three men, 43.0 ± 4.2 yr old, mean ± SE) received per os on two different days, at a 3 day-interval, in a random order, placebo or 250 mg of acipimox, an inhibitor of lipolysis analogous to nicotinic acid, at 0700 and 1100 h. In both tests GHRH (1–29 NH_2), 50 μg, was administered iv at 1300 h. Blood samples for GH, FFA, immunoreactive insulin (IRI), and glucose were taken from 0900 to 1500 h, and the time period considered for statistical analysis was 1200–1500 h, representative of steady-state condition for FFA, IRI, and glucose. Mean plasma FFA levels (1200–1500 h) were significantly lower after acipimox than after placebo (0.05 ± 0.01 *vs.* 0.17 ± 0.01 g/L, $P < 0.01$). In contrast, both mean basal GH levels (1200–1300 h) and the mean GH response to GHRH (GH Δ area, 1300–1500 h) were significantly higher after acipimox than after placebo (12.0 ± 1.9 *vs.* 7.8 ± 1.2 μg/L, $P < 0.01$; 2937 ± 959 *vs.* 1154 ± 432 μg/L·120 min, $P < 0.01$). The increase in both basal GH levels and GH Δ area occurred in all eight patients. Acipimox also reduced mean serum IRI (83 ± 12 *vs.* 112 ± 14 pmol/L) and blood glucose (5.1 ± 0.1 *vs.* 5.7 ± 0.1 mmol/L) levels, as compared with placebo ($P < 0.03$ or less). Eight acromegalic patients (group 2: six women and two men, 46.6 ± 5.7 yr old) underwent a constant iv 10% lipid infusion (150 mL/h), started at 0900 h and continued until 1500 h. Mean plasma FFA levels (1200–1500 h) were significantly higher during lipid infusion than after placebo (0.27 ± 0.01 *vs.* 0.16 ± 0.01 g/L, $P < 0.02$); in contrast, mean basal GH levels (1200–1300 h) were reduced by lipid infusion, as compared with placebo (9.9 ± 3.1 *vs.* 16.6 ± 4.4 μg/L, $P < 0.01$), and the same occurred for the GH Δ area after GHRH (2498 ± 1643 *vs.* 4512 ± 1988 μg/L·120 min, $P < 0.01$). Serum IRI and blood glucose levels were similar after placebo and during lipid infusion.

These data indicate that, in acromegaly, the acute reduction of circulating FFA levels results in increased GH release, whereas the increase in circulating FFA levels is accompanied by a reduced GH release. Taken together, these findings suggest that, in acromegaly, the control of FFA on GH release is preserved. (*J Clin Endocrinol Metab* **84:** 1234–1238, 1999)

GH SECRETION is regulated by two specific hypothalamic neurohormones, the stimulatory GHRH and the inhibitory SRIF (1). The release of these neurohormones, in turn, is modulated by a large cohort of neurotransmitters, peptides, hormones, and metabolic variables.

Acromegaly is a pathological condition characterized by elevated circulating GH levels, which are usually detectable at all times and fluctuate widely throughout the day (2, 3). High GH levels are attributable to GH hypersecretion that is caused, with few exceptions (4–6), by a pituitary adenoma, and do not depend on an alteration in the processes of GH distribution or disappearance (7). Several abnormalities have been reported in the mechanisms governing GH secretion in acromegalic patients. *In vivo* GH hypersecretion occurs in spite of high circulating insulin-like growth factor I (IGF-I) levels, indicating disruption of the negative IGF-I feedback on GH release (8). Furthermore, the GH response to the normally suppressive effect of hyperglycemia is variable, because GH levels may rise, be partially suppressed, or not change after an oral glucose load (9, 10). In addition, there is often paradoxical responsiveness to L-dopa (11) and dopamine agonists (12, 13), and to stimuli that do not affect GH release in normal subjects [TRH, GnRH, CRH, vasoactive intestinal peptide (VIP), peptide histidine methionine)] (14–18). In the majority of acromegalic patients, however, circulating GH levels decrease after administration of SRIH and its analogs (19–21). This finding supports the hypothesis that, in acromegaly, GH secretion is not completely autonomous but is under some degree of hypothalamic regulation. Data obtained *in vitro* in static incubations (22, 23) and via perifusion systems (24) also indicate that most GH-secreting pituitary adenomas maintain, at least qualitatively, a normal sensitivity to the hypothalamic regulatory hormones GHRH and SRIH and also to the peripherally generated IGF-I and insulin (25).

In this complex and variable pathophysiologic circumstance, we are unaware of any information about the effects of free fatty acids (FFA). FFA exert a negative feedback on GH release under physiological conditions (26–31). To investigate whether the FFA-negative feedback on GH release persists in acromegaly, we designed a placebo-controlled study in which GH release was analyzed after: 1) acute reduction of circulating FFA levels by pharmacologic blockade of lipolysis; and 2) acute increase of circulating FFA levels induced by iv lipid infusion.

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Subjects and Methods

Subjects and experimental procedures

The protocol for the study was approved by the local ethics committee. Fifteen consecutive acromegalic patients, hospitalized at Ospedale San Raffaele (10 women and 5 men), were admitted to the study after giving written informed consent. Subjects characteristics are shown in Table 1. Diagnosis of active acromegaly was based on the clinical picture, failure of GH levels to suppress under 2 μg/L after an oral glucose load, and elevated plasma IGF-I levels. All acromegalic patients had a pituitary adenoma, by magnetic resonance imaging, confirmed at surgery.

Following an experimental protocol, previously designed by our group to investigate the interplay GH/FFA in normal subjects (27, 28), the first eight acromegalic subjects (group 1 of Table 1) received (per os, on two different days, at a 3 day-interval, and in a random order) placebo or 250 mg acipimox (Olbetam, Pharmacia & Upjohn, Inc., Milan, Italy) at 0700 h and at 1100 h. Acipimox is an inhibitor of lipolysis analogous to nicotinic acid that is known to act only on the adipose tissue (32, 33). In both tests, GHRH (1–29 NH_2), 50 μg iv, was administered at 1300 h.

Patients no. 9–15 (group 2 of Table 1) underwent (on two different days, at a 3-day interval, and in random order) a 0.9% NaCl infusion or a constant lipid infusion (Intralipid 10%) (31) at the rate of 150 mL/h, started at 0900 h and continued until 1500 h. GHRH (50 μg, iv) was administered at 1300 h. Patient no. 7 underwent both tests, with acipimox or lipid infusion, and was therefore included in both groups.

In each test, blood samples for evaluation of serum GH levels were taken every 10 min, from 0900 h to 1300 h (time of GHRH injection) and 15, 30, 45, 60, 90, and 120 min after, via an indwelling catheter inserted into a forearm vein at least half an hour before the beginning of the sampling period. Blood samples for evaluation of plasma FFA, serum insulin [immunoreactive insulin (IRI)], and blood glucose levels were taken every 30 min throughout each study.

Patients no. 1, 4–8, and 10–15 also underwent a TRH test (200 μg, iv), with blood samples for GH taken at 0, 15, 30, 45, 60, 90, and 120 min. On the day of each test, all subjects were fasted overnight and remained recumbent throughout the test.

Assays

Plasma FFA levels were measured by a spectrophotometric method adapted to Cobas-Fara 2 (Roche, Basel, Switzerland) using kits supplied by Italfarmaco (Milano, Italy). Intra- and interassay coefficients of variations (CVs) were 2.3 and 3.1%, respectively. Serum IRI levels were measured by RIA using kits supplied by INCSTAR Corp. (Stillwater, MN). The minimum sensitivity of the assay was 13 pmol/L, and intra- and interassay CVs were 3.9 and 8.9%, respectively. Serum GH levels were measured by RIA using kits supplied by Farmos Diagnostic (Turku, Finland). The minimum sensitivity of the assay was 0.2 μg/L, and the median intra- and interassay CVs for GH concentrations, ranging from 0.2–50 μg/L, were less than 9 and 10%, respectively. Blood glucose levels were measured by a glucose oxidase method (Glucose Analyzer II, Beckman Coulter, Inc. Instruments, Fullerton, CA).

Calculations and statistical analysis

For all the variables, statistical analysis was performed for the interval 1200–1500 h. From 1200 h, in fact, steady-state conditions for plasma FFA, serum IRI, and blood glucose levels were evident in all tests and were maintained until 1500 h. Mean basal GH levels therefore represent the mean of seven samples between 1200 and 1300 h. The integrated GH response to GHRH (GH Δ area) was calculated, by the trapezoidal method, over the 2 h after GHRH injection (1300–1500 h). Because of the nonnormal distribution of the data (assessed by the Kolmogorov-Smirnov test), the comparisons of both basal GH levels and the GH Δ areas after placebo/acipimox (group 1) and placebo/lipid infusion (group 2) were performed by the nonparametric Wilcoxon signed-rank test. Comparisons of mean plasma FFA, blood glucose, and serum IRI levels (mean of seven samples between 1200 h and 1500 h) were performed by the Student's *t* test for paired data. The Pearson product-moment correlation coefficient was used to evaluate the degree of correlation between all parameters reported in *Results*.

Results

Figure 1 represents plasma FFA and serum GH levels between 1200 h and 1500 h in patients of group 1, receiving placebo or acipimox at 0700 and 1100 h. In all eight patients, mean plasma FFA levels were significantly lower after acipimox than after placebo. The acute reduction of plasma FFA levels induced by acipimox was accompanied by a significant increase of both basal serum GH levels and of the GH response to GHRH (GH Δ area). Numeric values and statistical comparisons for all the variables are reported in the *left* panel of Table 2. Acipimox administration, besides significantly reducing plasma FFA levels and increasing GH levels, also induced a significant decrease of mean serum IRI and blood glucose levels.

In subjects of group 2, lipid infusion (started at 0900 h)

TABLE 1. Clinical details of acromegalic patients

Subjects	Sex/age (yr)	Weight (kg)	BMI (kg/m^2)	Size of the tumor
Group 1				
1	M/34	88	25.1	Microadenoma
2	M/48	107	33.4	Microadenoma
3	F/57	70	25.9	Microadenoma
4	M/28	95	26.3	Macroadenoma
5	F/39	72	30.0	Macroadenoma
6	F/40	68	25.1	Macroadenoma
7	F/63	83	27.6	Microadenoma
8	F/35	88	33.8	Microadenoma
mean ± SE	43.0 ± 4.2	83.8 ± 4.7	28.4 ± 1.2	
Group 2				
7	F/63	83	27.6	Microadenoma
9	F/32	70	28.0	Macroadenoma
10	F/64	60	24.0	Macroadenoma
11	F/65	73	29.2	Microadenoma
12	M/53	77	27.5	Microadenoma
13	F/37	64	22.8	Macroadenoma
14	F/26	67	24.8	Macroadenoma
15	M/33	99	33.0	Microadenoma
mean ± SE	46.6 ± 5.7	74.1 ± 4.3	27.1 ± 1.1	

BMI, Body mass index.

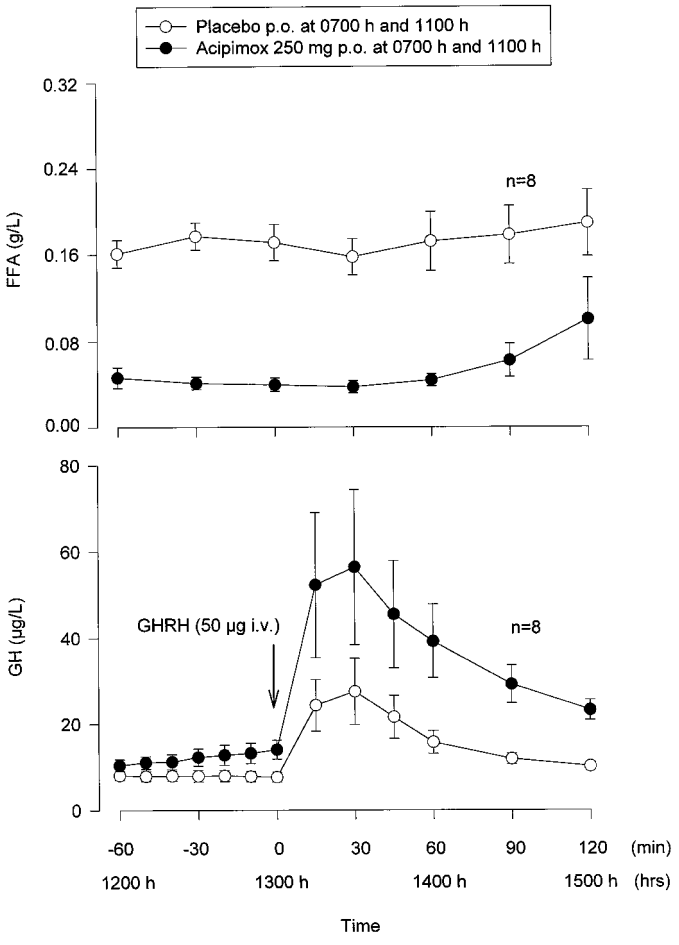

FIG. 1. *Upper* panel, Plasma FFA levels (1200–1500 h), after oral placebo and acipimox administration (0700 and 1100 h), in eight acromegalic subjects of group 1; *lower* panel, basal serum GH levels and GH response to GHRH, after placebo and acipimox administration, in the same subjects.

progressively increased circulating FFA levels, so that by 1200 h, a new steady-state for plasma FFA was reached, and maintained until 1500 h (Fig. 2, *upper* panel). In all subjects of group 2, the increase in plasma FFA levels was accompanied by a concomitant significant reduction of basal serum GH levels, as well as of the GH Δ area (Fig. 2, *lower* panel). Numeric values and statistical comparisons for all the variables are reported in the *right* panel of Table 2. Mean serum IRI and blood glucose levels remained unaffected by lipid infusion. To clarify the effect of acipimox administration and of lipid infusion on GH levels in acromegaly, the GH profiles of subject no. 7 (who underwent tests with placebo, acipimox, and lipid infusion) are shown in Fig. 3.

Table 3 reports a qualitative comparison between the GH response to GHRH after placebo or acipimox, and during lipid infusion, and that to TRH after placebo (positive response: GH Δ peak, *i.e.* GH increment above basal levels, >50%). After placebo, patients of both groups showed a variable response to TRH and GHRH. In addition to the significant increase in GH Δ area after acipimox (Table 2), all subjects of group 1 showed a qualitatively positive response to GHRH (Table 3, *upper* panel). In all subjects of group 2, GH Δ peak after GHRH was reduced by lipid infusion; however, five of eight subjects, responsive after placebo, continued to be responsive also at higher plasma FFA levels (Table 3, *lower* panel).

In both groups of acromegalic patients, no correlations were found between mean FFA levels, basal GH levels, and the GH response to GHRH, after either placebo, acipimox administration, or lipid infusion.

Discussion

Among the abnormalities in the control of GH secretion that have been described in acromegaly, refractoriness to the glucose inhibiting effect (9, 10) and the paradoxical responsiveness to several stimuli (11, 14–18) have been widely used as tools for diagnosis and postoperative evaluation. We are unaware of any data, however, regarding the persistence of FFA-negative feedback on GH release in acromegaly.

The results of the present study indicate that, in acromegaly, as in nonacromegalic subjects (26–31), the acute reduction of circulating FFA levels results in increased GH release, whereas an increase in circulating FFA levels is accompanied by a reduced GH release. Of note is that enhancement of GH release after acipimox was evident in all patients, both qualitatively and quantitatively. On the other hand, lipid infusion decreased GH release in all patients, but five of eight of them continued to be responsive to GHRH (GH Δ peak > 50%). This could reflect a higher sensitivity of the adenoma cells to a decrease, rather than to an increase in circulating FFA levels. In any case, taken together, our findings suggest that, in acromegaly, GH-secreting adenomatous pituitary cells maintain their sensitivity to the negative control exerted by FFA.

These data are in agreement with previous reports indicating that GH secretion is not completely autonomous in acromegaly (19–25). Particularly, the normal (at least qualitatively) sensitivity to SRIH in most GH-secreting pituitary adenomas (19, 20, 22–24) may explain, in part, the persistent inhibitory effect of FFA on GH release in acromegaly, because experimental evidence suggests that FFA may trigger SRIH release from the hypothalamus (34). Other explanations include the persistence of the direct FFA inhibitory effect on the GH-secreting adenoma cells. Experimental evidence indicates that FFA may exert a nonselective blockade of spontaneous, as well as of GHRH-, TRH-, and VIP-stimulated GH release, directly at the pituitary (35–39). At this level, the main target for the biological actions of FFA seems to be the cellular membranes of the somatotrophs, via a perturbation of the lipid bilayer and a disruption of the lipid-lipid and lipid-protein interaction. Because plasma-borne FFA molecules are not covalently linked in the plasma membranes, but are included in the bilayer as wedges (40), they may fluctuate. Therefore, a change in the gradient of FFA from plasma toward cell membranes (as induced by acipimox and lipid infusion in this study) is able to modify the membrane FFA content (41) and to affect many biological functions, including cell-to-substrate adhesion, surface receptor capping, and transmembrane signaling (42–45).

Relevant to our study are previous findings indicating that caprylic acid and *cis*-unsaturated FFA are able to reduce

TABLE 2. Experimental parameters after placebo or acipimox (group 1) and after placebo and during lipid infusion (group 2)

Group 1				Group 2			
Parameters	Treatment		*P*	Parameters	Treatment		*P*
	Placebo	Acipimox			Placebo	Lipid infusion	
Mean FFA levels (g/L)	0.17 ± 0.01	0.05 ± 0.01	<0.01	Mean FFA levels (g/L)	0.16 ± 0.01	0.27 ± 0.01	<0.02
Mean basal GH levels (μg/L)	7.8 ± 1.2	12.0 ± 1.9	<0.01	Mean basal GH levels (μg/L)	16.6 ± 4.4	9.9 ± 3.1	<0.01
GH Δ area (μg/L·120 min)	1154 ± 432	2937 ± 959	<0.01	GH Δ area (μg/L·120 min)	4512 ± 1988	2498 ± 1643	<0.01
Mean IRI levels (pmol/L)	112 ± 14	83 ± 12	<0.03	Mean IRI levels (pmol/L)	105 ± 18	126 ± 19	ns
Mean glucose levels (mmol/L)	5.7 ± 0.1	5.1 ± 0.1	<0.01	Mean glucose levels (mmol/L)	5.6 ± 0.3	6.2 ± 0.6	ns

ns, Not significant.

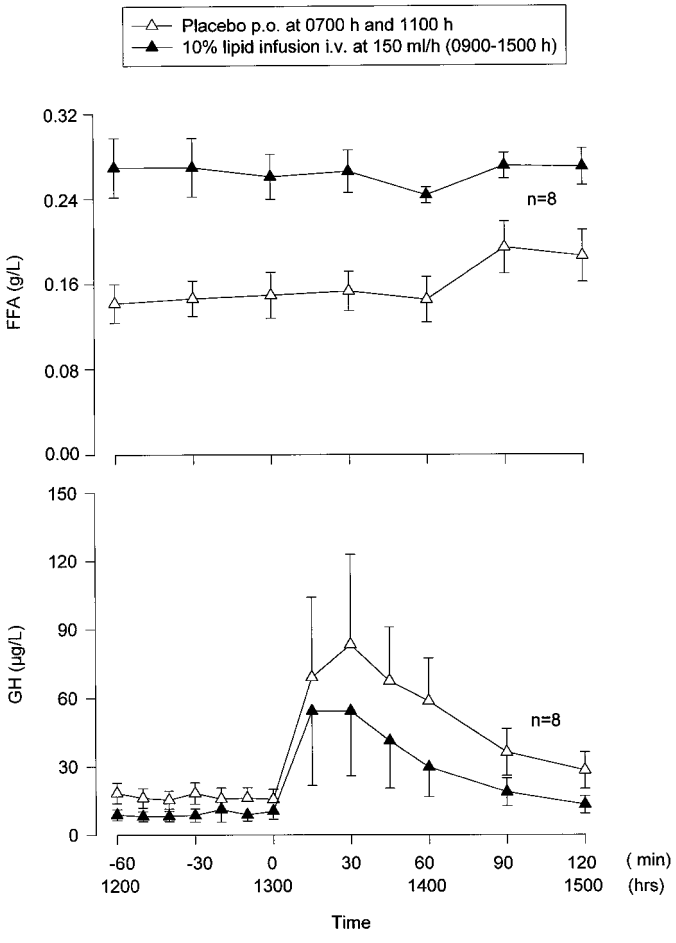

FIG. 2. *Upper* panel, Plasma FFA levels (1200–1500 h), after oral placebo (0700 and 1100 h) and during iv 10% lipid infusion, in eight acromegalic subjects of group 2; *lower* panel, basal serum GH levels and GH response to GHRH, after placebo and during lipid infusion, in the same subjects.

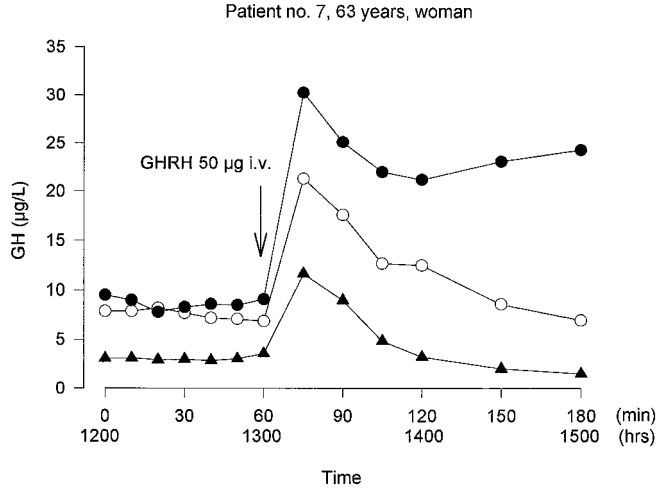

FIG. 3. Basal serum GH levels and GH response to GHRH in a single representative acromegalic subject (no. 7) after oral placebo (○) and acipimox (●) administration and during iv 10% lipid infusion (▲). Acipimox enhanced, and lipid infusion reduced both basal and GHRH-stimulated GH release, as compared with placebo.

TABLE 3. Qualitative analysis of the GH response to TRH and to GHRH (GH Δ peak) after placebo and acipimox, and during lipid infusion in acromegalic patients of groups 1 and 2

	TRH (200 μg iv)	GHRH (50 μg iv)	
Group 1		Placebo	Acipimox
1	−	+	+
2	NP	+	+
3	NP	+	+
4	+	+	+
5	−	+	+
6	+	−	+
7	+	+	+
8	+	+	+
Group 2		Placebo	Lipid infusion
7	+	+	+
9	NP	+	−
10	+	+	+
11	−	−	−
12	+	+	+
13	−	−	−
14	+	+	+
15	+	+	+

NP, Not performed. '+', GH increment >50% above basal levels; '−', <50% above basal levels.

GHRH- and VIP-stimulated GH release of cultured pituitary cells via a reduction, at least in part, of the adenylate cyclase activity (36, 39). In fact, it is known that about 40% of GH-secreting pituitary adenomas show a constitutive activation of the adenylate cyclase-cAMP system, caused by a point mutation in the α-subunit of the Gs protein linked to the adenylate cyclase coupled with the GHRH receptor (46). In our preliminary study, the mutation of the Gs protein has not been evaluated in any of the acromegalic patients. Our finding that, in all acromegalic patients examined, the GHRH-stimulated GH release was increased (or even became evident when absent after placebo) after acipimox, and was reduced by lipid infusion, needs therefore to be reconsidered in relation to such a mutation. The finding that FFA could persistently regulate GH release in response to GHRH, also

in the presence of the so-called *gsp* oncogene, could, in fact, bring new insights regarding the intracellular mechanisms involved in the FFA control of GH release. In this regard, it could also be of interest to examine, in acromegalic patients, the influence that FFA may exert on the GH release induced by stimuli acting via pathways other than the adenylate cyclase-cAMP system, such as TRH.

In conclusion, our preliminary data indicate that, in acromegaly, the acute reduction of circulating FFA levels results in increased GH release, whereas the increase in circulating FFA levels is accompanied by a reduced GH release. Taken together, these findings indicate that, in acromegaly, the control exerted by FFA on GH release is preserved. Further studies are needed to investigate the mechanisms involved, which may provide new insight about the pathophysiology of GH release in acromegaly.

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