Inhibitory Effects of Galanin on Growth Hormone (GH) Release in Cultured GH-Secreting Adenoma Cells: Comparative Study With Octreotide, GH-Releasing Hormone, and Thyrotropin-Releasing Hormone

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The aim of the present study was to characterize in a large series (N = 12) of cultured somatotrope adenomas the in vitro effects of the neuropeptide galanin on growth hormone (GH) secretion. This was contrasted with two peptides known to be GH secretagogues (GH-releasing hormone [GHRH] and thyrotropin-releasing hormone [TRH]) and a peptide with a known GH-inhibitory effect (the somatostatin analog octreotide). Groups of three wells were incubated for 4 hours with growth medium alone (control incubation), galanin, GHRH(1-29)NH_2, TRH, or octreotide. Galanin and octreotide were applied at concentrations of 0.1, 1, and 10 μmol/L, and GHRH and TRH at concentrations of 0.01, 0.1, and 1 μmol/L. Galanin was able to inhibit GH release in nine of 12 cultured somatotrope adenoma cells. This inhibitory effect was clearly dose-dependent in five adenomas. Overall, the mean GH nadir after galanin was −36.1% in nine responder adenoma cultures versus control wells. Octreotide inhibited GH release in five of eight cultured somatotrope adenoma cells. The mean GH nadir after octreotide was −32.7% in five responder adenoma cultures compared with control wells. GHRH and TRH were able to stimulate GH release, respectively, in seven of 11 and in six of seven cultured somatotrope adenoma cells. The mean GH peaks after either GHRH or TRH in responder adenoma cultures were, respectively, +71.5% and +143.7% compared with levels in the control wells. In conclusion, the consistency and potency of the in vitro GH-inhibitory effect of galanin in a large series of somatotrope adenomas are at least similar to those of the most effective available GH-lowering agent, the somatostatin analog octreotide.

GALANIN is a 29–amino acid, straight-chain, biologically active peptide that has been hypothesized to be a neurotransmitter or neuromodulator in the central nervous system.[1] A physiological role for galanin in the regulation of growth hormone (GH) secretion in humans has recently been suggested. In fact, the neuropeptide only marginally influences the secretion of other pituitary hormones in man,[2] whereas it is able to elicit consistent and clear increases in circulating GH levels when administered in normal humans,[3] probably acting at the hypothalamic level.[4]

Somatotrope adenomas represent approximately 20% of pituitary adenomas and cause acromegaly due to GH hypersecretion.[5] Disturbances in the GH secretion of somatotrope adenoma cells, in addition to excessive basal secretion, may involve a lack of stimulation by GH-releasing hormone (GHRH), a paradoxical increase in GH after stimulation with thyrotropin-releasing hormone (TRH),[5] and a lack of inhibition after administration of somatostatin or somatostatin analogs such as octreotide in some adenomas.[6,7]

Recently, we demonstrated that in the majority of a large series of patients with active acromegaly, the same dose of galanin, which has a physiological GH-excitatory effect, caused a paradoxical decrease in serum GH levels.[8] This effect, which was variable in magnitude and timing between patients, was greater in acromegalic patients not cured after surgery than in untreated patients. On the other hand, in none of the surgically cured acromegalic patients did galanin maintain an inhibitory effect; in fact, in the large majority of this subgroup of patients, as well as in normal subjects, galanin had stimulatory effects on GH secretion.[8]

The mechanism underlying the galanin-mediated inhibition of GH secretion in acromegaly is still unknown. The working hypothesis is that galanin may act directly at the pituitary level through specific receptors expressed on the membranes of adenomatous cells. This hypothesis is also supported by the preliminary observation that galanin is able to decrease GH secretion in a rat GH-producing adenoma cell line.[9] The aim of the present study was to characterize the in vitro effects of galanin in a large series of cultured human somatotrope adenomas.

SUBJECTS AND METHODS

Patients

Pituitary adenoma tissues were studied from 12 patients with somatotrope tumors (numbered consecutively GH-oma 1 to GH-oma 12) obtained at transsphenoidal surgery. The presence of pituitary adenomas was confirmed by magnetic resonance imaging, and all patients had clinical and biochemical features of active acromegaly. GH-oma 4 was a recurrent adenoma from a patient who had undergone a first transsphenoidal intervention 7 years previously and had been treated with octreotide (150 μg three times daily) and bromocriptine (25 mg twice daily) for 5 years before the second surgical intervention. GH-oma 10 was from a patient who had undergone a first surgical intervention and conventional radiotherapy 28 years previously and had been treated with octreotide (100 μg three times daily) and bromocriptine (10 mg twice daily) over a period of 2 years before the second transsphenoidal operation. Clinical data for the patients are listed in Table 1. The patients underwent the following biochemical evaluations preoperatively: (1) (N = 12) baseline serum GH and insulin-like growth factor-I (on at least three different occasions) and prolactin assays; (2) (n = 8) intravenous infusion of synthetic porcine galanin (Inalco, Milan, Italy; 500 μg reconstituted in 2 mL saline) in 100 mL saline from −10 to 30 minutes; (3) (n = 8) intravenous bolus injection

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Table 1. Clinical Characteristics of 12 Patients With GH-Secreting Adenomas (GH-omas 1 to 12)

GH-oma No.	Age (yr)	Sex	Disease Duration (yr)	Adenoma Extension (NMR)	GH Levels				IGF-I (ng/mL)	PRL (ng/mL)	Pituitary Function
					Basal* (μg/L)	Nadir OGTT (μg/L)	Peak TRH (%)†	Nadir Galanin (%)†			
1	27	M	7	Intrasellar	4.1	3	195	ND	481	14	Normal
2	34	F	7	Intrasellar	20.4	4	ND	78	944	43	Normal
3	44	M	2	Intrasellar	10	4.1	323	89	850	6	Normal
4	37	F	9	Suprasellar	10	5.4	114	60	700	2	Hypogonadism
5	16	M	1	Intrasellar	21.6	15.1	1,400	82	1,997	108	Normal
6	61	F	6	Intrasellar/suprasellar	12	ND	330	65	1,130	5	Normal
7	41	M	10	Intrasellar	40	30	515	84	1,270	58	Normal
8	48	M	6	Intrasellar/suprasellar	3.7	4.8	116.2	ND	1,070	14	Normal
9	63	M	15	Intrasellar/parasellar	10.6	8	ND	ND	448	20	Hypogonadism, hypothyroidism
10	59	F	22	Intrasellar/suprasellar	21.8	ND	ND	84	812	24	Normal
11	25	F	1	Intrasellar	26.9	13.1	166	57	801	24	Hypogonadism
12	59	M	6	Intrasellar	20	ND	ND	ND	801	24	Normal

Abbreviations: ND, not determined; NMR, nuclear magnetic resonance; PRL, prolactin; IGF-I, insulin-like growth factor-I.
*Mean of 3 baseline samples.
†Expressed as % change *v* baseline.

of TRH (Serono, Milan, Italy; 200 μg at time 0); and (4) (n = 9) oral glucose tolerance test (OGTT) with administration of 75 g glucose orally at time 0. Blood samples for GH assays were taken at −15, −10, 0, 15, 30, 45, 60, 90, and 120 minutes during galanin and TRH tests and for GH and glucose assays at 0, 30, 60, 90, and 120 minutes during the OGTT.

Cell Cultures

Adenomatous tissue obtained after neurosurgery was washed with phosphate-buffered saline (PBS) and dissected into small pieces. The tissue fragments were mechanically and enzymatically dispersed using 0.25% trypsin and 0.02% EDTA at pH 7.3. Dispersed cells were centrifuged and resuspended in sterile culture medium. The cells were diluted with culture medium and plated in 24 plastic well plates (Costar, Cambridge, MA) at an initial concentration of 60,000 per well as previously reported.[7] The initial growth medium was Dulbecco's modified Eagle's medium supplemented with 10% fetal calf serum, 100 U/mL penicillin, 100 μg/mL streptomycin, 2.5 μg/mL amphotericin B (Fungizone; Bristol-Myers Squibb, Princeton, NJ), and 2 mmol/L glutamine. The cells were grown at 37°C in an atmosphere of 5% CO_2. After 3 days, the cells were washed three times with PBS, and fresh growth medium was added.

Incubation of the Cells With Test Substances

The effect of various neuropeptides on the GH-secreting cells was tested as follows. The experiments were conducted on cells 4 days after plating, when usually an 80% confluent monolayer was obtained. The growth medium was removed by aspiration, and the attached cells were washed several times with PBS. For the incubation experiments, we used Dulbecco's modified Eagle's medium (pH 7.3) supplemented with 10% fetal calf serum, 100 U/mL penicillin, 100 μg/mL streptomycin, 2.5 μg/mL Fungizone, and 2 mmol/L glutamine. Groups of three wells were incubated for 4 hours with growth medium alone (control incubation), porcine galanin, GHRH(1-29)NH_2 (Geref, Serono, Italy), TRH, or the somatostatin analog octreotide (Sandoz, Basee, Switzerland). All these peptides were diluted in the same medium and added at the following concentrations: galanin and octreotide, 0.1, 1, and 10 μmol/L, and GHRH and TRH, 0.01, 0.1, and 1 μmol/L. After an incubation period of 4 hours, which was hypothesized to be the optimal incubation time for all of the various test substances,[7-11] the supernatants were removed and stored frozen at −70°C until assayed for GH.

Due to the limited number of cells obtained from neurosurgical fragments, all experiments were performed in each somatotrope adenoma in random order on nonconsecutive days and within 10 days from the beginning of the study (this period was chosen to avoid excessive culture aging[12]).

Assays

Commercial kits were used for the estimation of GH (immunoradiometric assay, Allegro HGH; Nichols Institute, San Juan Capistrano, CA; interassay and intraassay coefficients of variation, ±5.4% and ±2.3%, respectively; sensitivity limit of the assay, 0.2 μg/L). All samples from the same subjects or adenomas were assayed together in duplicate.

Statistical Analysis

GH secretion rates in vitro are expressed as a percent of the control values, with the exception of Table 2, where basal GH secretion is expressed as micrograms per liter per 4 hours. For each adenoma, the inhibitory effect of a given substance was defined as a decrease in GH levels of at least 20% compared with control wells with at least two of three doses tested; the excitatory effect of a substance was defined as an increase in GH levels of at least 20% compared with control wells with at least two of three doses tested. Statistical analysis was performed using the Kruskall-Wallis test; P less than .05 was considered significant.

RESULTS

Correlations Between In Vitro and In Vivo GH Secretion

In vitro basal GH secretion varied from 3 (GH-oma 9) to 350 (GH-oma 11) μg/L/4 h. There was a significant correlation ($P < .05$) between basal GH secretion in vitro and plasma GH levels in vivo (Fig 1). However, no significant correlation was found between the percent inhibition of GH secretion obtained with galanin in vivo and in vitro.

In Vitro Effects of Inhibitory Peptides on GH Secretion

Galanin. Galanin was able to inhibit GH release in nine of 12 cultured somatotrope adenoma cells (75%). This inhibitory effect was clearly dose-dependent in five of adenoma cells (Fig 2); in these adenomas (GH-omas 2, 6, 8, 10, and 12), the greatest inhibitory effect of galanin was produced with the

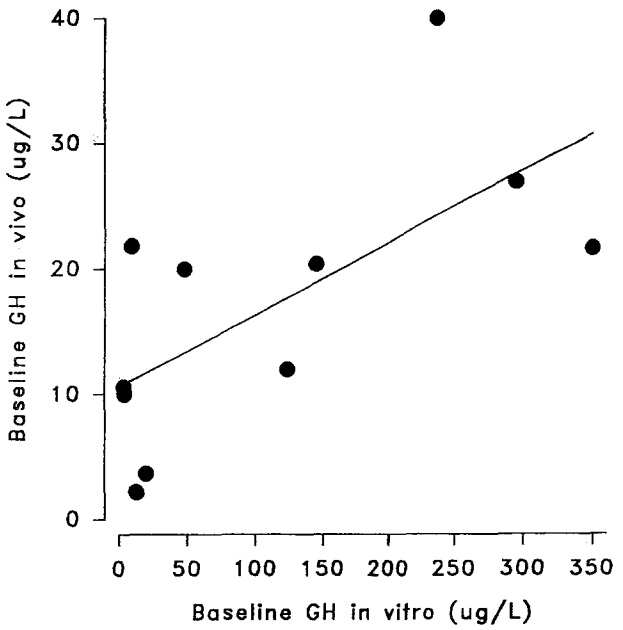

Fig 1. Correlations between in vivo and in vitro (4-hour control incubation period) GH secretion rates in 12 GH-producing adenomas ($r = .678$; $P = .015$).

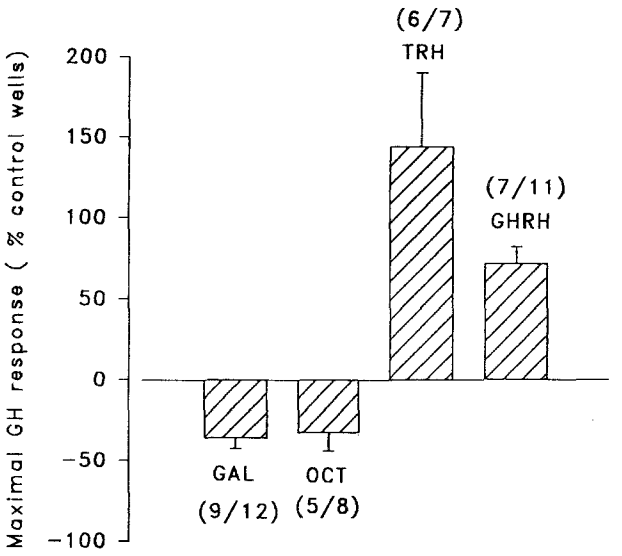

Fig 3. Maximal GH-inhibitory (GAL/OCT) or -excitatory (GHRH/TRH) effects (expressed as % of control wells, mean of 3 wells) in responder cultured GH-secreting adenoma cells. The number of responder adenomas from the total number of adenomas tested is reported for each substance in parentheses.

highest dose used (10 μmol/L). In the other four responder cultured adenoma cells, the greatest inhibition was measured already at either the 0.1-μmol/L (GH-oma 9) or 1-μmol/L (GH-omas 1, 4, and 5) concentration. Overall, the mean GH nadir after galanin in nine responder adenoma cultures, independently of the dose at which this was obtained, was −36.1% compared with levels in the controls (Fig 3). In the whole population of responder adenomas, the inhibitory effect became significant at 1 μmol/L (range, −60% to −20% *v* control wells) and was still significant at 10 μmol/L galanin (range, −52% to −20% *v* control wells). In three nonresponder adenomas, no significant changes in GH secretion (<−20% *v* control wells) were observed at any galanin concentration.

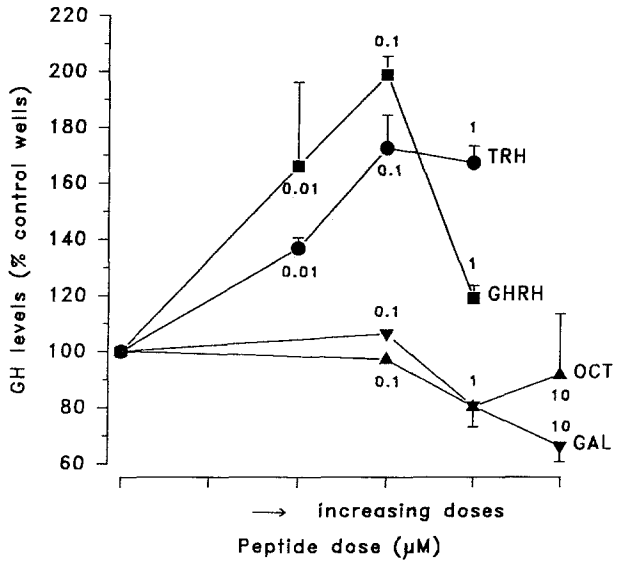

Fig 2. GH responses (expressed as % of control wells, mean of 3 wells) to two inhibitory substances, galanin (GAL, ▼) and octreotide (OCT, ▲) 0.1, 1, and 10 μmol/L and two excitatory substances, GHRH (■) and TRH (●) 0.01, 0.1, and 1 μmol/L in 1 of the tested GH-secreting adenomas (GH-oma 6) responding to all substances added to the culture medium.

Octreotide. Octreotide inhibited GH release in five of eight cultured somatotrope adenoma cells tested (63%), although in none of the adenomas was this inhibitory effect clearly dose-dependent (Fig 2). The mean GH nadir after octreotide in responder adenoma cultures, independently of the concentration at which this effect was obtained, was −33% versus the level in the controls (Fig 2). In the whole population of responder adenomas, the inhibitory effect was significant compared with baseline only at 1 μmol/L octreotide (range, −75% to −20% *v* control wells).

In Vitro Effects of Stimulatory Peptides on GH Secretion

GHRH. GHRH was able to stimulate GH release in seven of 11 cultured somatotrope adenoma cells tested (63.3%) (Fig 2). The mean GH peak after GHRH in seven responder adenoma cultures, independently of the concentration at which this was obtained, was +71.5% compared with the level in control wells (Fig 3). In the whole population of responder adenomas, the stimulatory effect became significant compared with baseline already at the concentration of 0.01 μmol/L GHRH (range, +20% to +83.3% *v* control wells) and reached a plateau at 0.1 μmol/L GHRH (range, +23.4% to +98% *v* control wells). Only in GH-oma 3 was the peak stimulatory effect obtained at the concentration of 1 μmol/L. In the other six cultured adenoma cells, maximal stimulation was obtained already at either 0.01 μmol/L (GH-omas 6, 7, and 8) or 0.1 μmol/L (GH-omas 2, 4, and 12).

TRH. TRH was able to stimulate GH release in six of seven tested cultured somatotrope adenoma cells (85.7%) (Fig 2).

This stimulatory effect was clearly dose-dependent in three of seven adenoma cells; in fact, in these adenomas (GH-omas 5, 7, and 9), the peak stimulatory effect of TRH was obtained with the maximal concentration used (1 μmol/L). In the other three cultured adenoma cells, the greatest stimulation was obtained already at either 0.01 μmol/L (GH-oma 3) or 0.1 μmol/L (GH-omas 6 and 11). Overall, the mean GH peak after TRH in six responder adenoma cultures, independently of the dose at which this effect was obtained, was +143.7% compared with the level in control wells (Fig 2). However, in the whole population of responder adenomas, the stimulatory effect was significant compared with baseline only at the maximal concentration of TRH (1 μmol/L; range, +31% to +200% *v* control wells).

Correlations Between In Vitro Effects of Galanin and Other Tested Peptides

Galanin was able to inhibit GH secretion in nine of 12 adenomas tested; GH-omas 3, 7, and 11 were classified as nonresponders. The other inhibitory peptide used in our experiments, octreotide, inhibited GH secretion in five of eight adenomas tested. The three adenomas classified as nonresponders to octreotide (GH-omas 4, 5, and 9) were all responders to galanin, whereas two of three nonresponder adenomas to galanin were responders to octreotide (GH-omas 3 and 7; GH-oma 11 not tested with octreotide) (Table 2). Overall, all of the adenomas tested were inhibited by at least one of the two peptides. In only three instances (GH-omas 6, 8, and 10) was GH secretion inhibited by both substances. TRH stimulated GH secretion in six of seven adenomas tested. Three of these adenomas (GH-omas 5, 6, and 9) were responders to galanin. Conversely, adenomas that were not inhibited by galanin were all responders to TRH. GHRH was able to stimulate GH secretion in seven of 11 adenomas tested. In five instances (GH-omas 2, 4, 6, 8, and 12), GH secretion was inhibited by galanin. On the other hand, three of four adenoma nonresponders to GHRH were inhibited by galanin. Finally, two of three adenomas defined as nonresponders to galanin were classified as responders to GHRH (Table 2).

Table 2. Qualitative Definition of In Vitro GH Responses to Four Tested Substances, Galanin, Octreotide, GHRH, and TRH, in 12 GH-Secreting Adenomas

GH-oma No.	Basal GH Secretion (μg/L/4 h)	Response In Vitro to			
		GAL	OCT	TRH	GHRH
1	12.5	+	ND	ND	ND
2	145	+	ND	ND	+
3	3.8	−	+	+	+
4	3.8	+	−	ND	+
5	350	+	−	+	−
6	123.6	+	+	+	+
7	237	−	+	+	+
8	19.5	+	+	−	+
9	3	+	−	+	−
10	8.8	+	+	ND	−
11	295.1	−	ND	+	−
12	47.7	+	ND	ND	+

Abbreviations: ND, not determined; GAL, galanin; OCT, octreotide; GAL and OCT: +, ≥20% inhibition *v* control wells with 2 of 3 doses tested; GHRH and TRH: +, ≥20% stimulation *v* control wells with 2 of 3 doses tested.

No significant correlations were found between the inhibitory effects of galanin and octreotide in cells responding to both peptides. The inhibitory effects of galanin did not correlate with the magnitude of the stimulatory effect of either GHRH or TRH when cells sensitive to these peptides were considered.

DISCUSSION

The neuropeptide galanin increases GH secretion,[2,3,13] acting physiologically in vivo at the hypothalamic level via either GHRH or somatostatin.[14] Pretreatment of conscious rats with anti-GHRH antibodies blocks the GH increase induced by intravenous and intraventricular galanin infusion.[14,15] We have previously reported that a paradoxical GH-inhibitory response to galanin may be observed in approximately 90% of a large series of patients with active acromegaly, whereas patients thought to be cured are not likely to have an inhibitory response to galanin.[8] The mechanism through which this paradoxical GH-inhibitory effect of galanin may take place in active acromegaly is still to be clarified. Recently, adenomatous tissue obtained during neurosurgery in four patients was cultured in vitro, and the effect of galanin on GH-secreting cells was tested. In three of four adenomas examined, galanin produced a clear dose-dependent decrease in GH secretion. In the remaining adenoma, no clear inhibiting effects of the peptide were observed. Overall, galanin caused a significant decrease compared with baseline in the mean GH secretion of the four adenoma cells only at the dose of 1 μmol/L. In three adenoma cell populations showing a clear paradoxical GH inhibition after galanin treatment, the maximal galanin-induced percent GH decrease compared with control wells ranged from −60% to −19.7%.[8] On the basis of this preliminary observation, it was hypothesized that galanin may exert its GH-inhibitory effect in acromegaly by acting directly at the adenoma tissue level.

Therefore, the aim of our study was to ascertain the incidence and phenotype of the in vitro GH-inhibitory effect of galanin in a new and large series of GH-secreting cultured adenomas. The mechanism of the inhibitory action of galanin in vitro was also investigated by comparing its action with that of GHRH, TRH (excitatory substance), and the somatostatin analog octreotide (inhibitory substance) in the same adenoma cells.

Our data show that at least a certain degree of inhibition of serum GH may be observed with galanin in greater than 70% of cultured GH-secreting adenomas (nine of 12). A large variability in the magnitude of this GH-inhibitory effect of galanin was observed; in fact, the maximal nadir of serum GH levels ranged from −60% to −20% of the levels in the control wells, with a mean maximal inhibitory effect of −36%. These data confirm the results of our preliminary study in GH-secreting adenomas in terms of both the incidence and magnitude of the inhibitory effect of galanin.[8] GH hypersecretion in acromegaly can often be reduced by medical treatment with the somatostatin analog octreotide.[16] On the other hand, in some patients with acromegaly in vivo and in some GH-secretory adenomas in vitro, GH secretion is not inhibited by octreotide.[6,7] The different responses of somatotrope adenomas to somatostatin and its

analogs have recently been suggested to be associated with the different expression of various somatostatin receptor subtypes that differ in the affinity to somatostatin or somatostatin analogs.[17]

In our study, basal GH secretion in five of eight somatotrope adenoma cell cultures could be inhibited by octreotide. These data are consistent with previously reported data in a large series of GH-secretory adenomas showing a similar incidence of responder cells to octreotide.[7] Interestingly, in our study, the three adenomas defined as nonresponders to octreotide were clearly inhibited by galanin. In contrast, two of three adenomas defined as nonresponders to galanin were inhibited by octreotide. Overall, the inhibitory potency both in qualitative and in quantitative terms was slightly but not significantly higher with galanin compared with octreotide. These observations have interesting potential pathophysiological and clinical impact. In fact, it can be hypothesized that galanin may be able to interact with somatostatin receptor subtypes other than subtype 2, which is known to interact with octreotide.[18] In fact, in only a minority of the tested adenomas (three of 12) was GH inhibition obtained with both galanin and octreotide (those adenomas could be thought to express different somatostatin receptor subtypes). Alternatively, it may be suggested that galanin may interact on the GH-adenoma cell membranes with its own receptors, which are not expressed by normal somatotropes. It has been shown that the galanin receptor, which has recently been cloned in a human melanoma cell line,[19] is a glycoprotein of 54 kd coupled to the inhibitory guanine nucleotide binding protein G_i.[20] Moreover, galanin has been shown to be a weak direct GH secretagogue in normal rat somatotropes cultured in vitro and to cause a paradoxical inhibition of GH release in a rat adenomatous GH-secreting cell line (GH_1).[9] Therefore, it can be hypothesized that in some human GH-secreting adenoma cells, either a native or mutant galanin receptor, but not the receptor for somatostatin, may be expressed and mediate the inhibitory effect of the neuropeptide. Finally, our data do not exclude that galanin and octreotide may share a similar intracellular signal transduction pathway in somatotrope adenomas, ie, cyclic adenosine monophosphate.[21,22] The potential clinical relevance of our data may be the finding that all the adenomas considered nonresponders to octreotide are consistently inhibited by galanin. Therefore, one can hypothesize a potential role for putative long-acting analogs of galanin in the treatment of acromegalic patients who are nonresponders to octreotide.[16]

We have previously shown that in active acromegaly, there is an inverse correlation between the magnitude of the opposite effects of galanin (inhibition) and TRH (stimulation). This finding suggested that galanin may have mechanisms of action opposite to those of TRH at the intracellular level.[8] Our present data do not seem to support this hypothesis, showing concordance between the inhibitory effects of galanin and the stimulatory effects of TRH in only three of 12 adenomas tested. Since TRH is known to increase intracellular calcium and to stimulate phosphatidylinositol turnover in pituitary adenomas,[23] it does not seem likely that galanin exerts its action in acromegaly via either calcium or phosphatidylinositol pathways.

In GH-secreting adenomas, the lack of a stimulatory effect of GHRH on GH secretion has been correlated with expression of the *gsp* oncogene.[24] Expression of this oncogene leads to a constitutive activation of the adenylate cyclase system, and because GHRH mediates GH secretion via this signal transduction system, GH secretion is not or is only poorly stimulated by GHRH.[25] Our data are consistent with previously reported evidence that approximately 40% of somatotrope adenomas express the *gsp* oncogene[24,25]; in fact, four of 11 adenomas tested were nonresponders to GHRH (36%). Three of four nonresponder adenomas to GHRH were effectively inhibited by galanin. Therefore, by extrapolation, it would seem that galanin is able to inhibit GH secretion in both *gsp*-negative and *gsp*-positive adenoma cells, and that the action of galanin is not linked to the GHRH receptor. However, our data showing a good qualitative correlation between the stimulatory effect of GHRH and the inhibitory effect of galanin seem to suggest that the action of galanin may be dependent on opposite changes in intracellular cyclic adenosine monophosphate as compared with GHRH.[25] In conclusion, galanin was able to inhibit GH secretion in 75% of human somatotrope adenoma cell cultures investigated by us. The consistency and potency of this in vitro inhibitory effect of galanin are at least similar to those of the most effective available GH-lowering agent, the somatostatin analog octreotide.

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