Rhinology, 22, 125-131, 1984

Growth activities of the nasal septal cartilage in acromegaly

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SUMMARY

Growth activity in different areas of human septal cartilage was measured by in vitro incorporation of 35 S-labelled sulfate and 3 H-labelled thymidine in 6 acromegalic patients. Septal cartilage was obtained during transnasal hypophysectomy. The growth activities in the posterior area, which is situated anterior to the septo-ethmoidal junction were significantly enhanced compared to a control group of hormonally normal adults. Growth activities of the septal cartilage in the anterior free end and the suprapremaxillary area were not different in both groups. This indicates that growth hormone excess in acromegaly enhances human septal growth by stimulation of growth activities in the posterior area and not at the anterior free end and suprapremaxillary area.

INTRODUCTION

Acromegaly is an endocrine disease due to growth hormone excess originating from somatroph adenoma of the pituitary gland. The early clinical features of acromegaly are coarsening of the facial contours and soft tissue swelling of the feet and the hands. There is an enlargement of the tongue, increase in body hair and size, and number of sebaceous and sweat glands. On radiographs bony proliferation of the skull, mandible, of hands and feet is observed. The ribs continue to elongate because of proliferation at the cartilage-bone junction. Cartilage proliferation of the larynx results in a deep voice.

In the face many patients with acromegaly complain of excessive nasal growth. These nasal and facial deformities can be corrected by plastic surgery (Converse et al., 1978). Kinnman (1976) reported a regression of the nasal soft tissues swelling following successful removal of the somatotroph pituitary adenoma. However, no data are available on the growth mechanism of the nose and especially of the septal cartilage in acromegalic patients.

Therefore growth activities by in vitro incorporation of labelled sulfate and thymidine into different areas of the septal cartilage were investigated in these patients and compared to hormonally normal adults.

Table 1. Clinical data of 6 acromegalic patients. The normal fasting level of growth hormone is < 15 mU/l.

patient	sex	age (years)	fasting GH level (m U/l)	diameter and stage of adenoma	nasal enlargement	septal deviation
H.D.	f	22	160	20 mm, ademona II	+	+
A.J.	f	60	26	12 mm, cystic adenoma II	+	++
M.R.	m	27	75	15 mm, adenoma II	+	++
W.M.	f	50	59	12 mm, localized invasive adenoma III	+	++
A.Js.	f	29	30	8 mm, microadenoma I	+	(+)
S.A.	f	58	60	6 mm, microadenoma I	+	+

PATIENTS

The pertinent clinical data of 6 acromegalic patients are summarized in Table 1. Sex, age at diagnosis, fasting growth hormone (GH) level, diameter and stage of adenoma (Hardy, 1973), extent of nasal enlargement and septal deviation are presented. Septal cartilage was obtained during transseptal transsphenoidal pituitary surgery. The transseptal approach to the sella turcica was performed by an ENT-surgeon via hemitransfixion of the columella or sublabial incision. The applied surgical technique is a modification of the "maxilla-premaxilla" approach to extensive surgery of the nasal septum (Cottle et al., 1958) and has been described in detail by Kern and Laws (1978). As soon as the sphenoid tissues was reached the neurosurgeon continued to remove the somatotroph pituitary adenoma.

10 hormonally normal adults who underwent septal correction because of septal deviation served as control. Their precise data have been published recently (Vetter et al., 1984).

METHODS

The cartilaginous specimens from three different anatomical septal areas (anterior free end, suprapremaxillary area and posterior area) were analyzed for cell replication and matrix synthesis. Cell replication was measured by in vitro incorporation of 3 H-labelled thymidine which represents DNA synthesis, whereas the extent of matrix synthesis was measured by in vitro incorporation of 35 S-labelled sulfate into cartilage which represents the last step in proteoglycane synthesis. Both reactions are dependent on somatomedin, a cellular growth factor. Therefore all in vitro experiments were done in presence of somatomedin containing human serum. Immediately after surgery the septal cartilage was stripped of adherent perichondrium and cut into small pieces of a mean dry weight of 0.1 mg.

Thereafter parallel experiments of measuring proteoglycane synthesis and cell replication were started.

a. Proteoglycane synthesis

The single cartilaginous specimens were incubated for 48 hours at 37 °C in 200 µl of a solution containing 20 percent human pooled serum, 0.5 M sodium sulfate, amino acids (Hall, 1972) and 0.5 µCi 35 S-labelled sodium sulfate. Preliminary experiments revealed that the uptake of 35 S-labelled NaSO4 was proportional at different dose levels of pooled human serum (2.5, 5, 10 and 20 percent respectively). Therefore the highest tested serum concentration was used to get the optimal response of 35 S-uptake. After the incubation the cartilaginous specimens were washed with running tap water for two hours. After drying the washed specimens were hydrolyzed in concentrated formic acid at 70 °C for three hours. Then 10 ml of Bray solution was added and the incorporated radioactivity was counted in a liquid scintillation counter.

b. Cell replication

The single cartilaginous specimens were incubated for 48 hours at 37 °C in 200 µl of a solution containing 20 percent human pooled serum, amino acids (according to Hill 1979) and 1.5 µCi 3 H-labelled thymidine. Preliminary experiments revealed that the incorporation of 3 H-labelled thymidine was proportional at different dose levels of pooled human serum (2.5, 5, 10 and 20 percent respectively). Therefore the highest tested serum concentration was used to get the optimal response of thymidine incorporation. After the incubation the cartilaginous specimens were washed with running tap water for two hours. After drying the specimens were hydrolyzed in concentrated formic acid at 70 °C for three hours. Then 10 ml of Bray solution was added and the incorporated radioactivity was counted in a liquid scintillation counter.

Statistics

For each age group and each area of the septal cartilage, the mean and its 5% confidence interval of the growth activity were determined. The confidence interval is a measurement for the accuracy of the mean determining that with a probability of 95%, the true value of the mean is within the interval. Therefore, a significant difference in the growth activity of two areas exists if the confidence intervals of these areas do not overlap.

RESULTS

In Table 2 and 3 the individual data of 35 S-labelled sulfate and 3 H-labelled thymidine incorporation into cartilage of the 6 acromegalic patients are presented in comparison to the mean values of 10 normal adults. In addition Figure 1

Table 2. ^{35}S-sulfate incorporation (counts/min/0.1 mg dry weight of cartilage) in three areas of the septal cartilage of 6 acromegalic patients.

patient	anterior end	suprapremaxillary area	posterior area
H.D.	3200	1200	3050
A.J.	2430	1040	3130
M.R.	3400	1250	2660
W.M.	3030	1670	2940
A.Js.	4220	1450	3610
S.A.	1810	1270	2080
m ± 2 SD	3015 ± 830	1310 ± 220	2910 ± 510
normal adults (m ± 2 SD)	3700 ± 600	1380 ± 230	1550 ± 250

Table 3. ^{3}H-thymidine incorporation (counts/min/0.1 mg dry weight of cartilage) in three areas of the septal cartilage of 6 acromegalic patients.

patient	anterior end	suprapremaxillary area	posterior area
H.D.	2600	1680	4200
A.J.	4120	1000	3160
M.R.	3460	1720	3420
W.M.	4630	1360	-
A.Js.	3220	1250	2890
S.A.	2850	1660	2820
m ± 2 SD	3480 ± 770	1189 ± 560	3298 ± 500
normal adults (m ± 2 SD)	3560 ± 480	1580 ± 360	1890 ± 210

summarizes the results in normal and acromegalic patients.

In the posterior area of the septal cartilage sulfate and thymidine incorporation was significantly elevated in each of the acromegalic patients compared to the healthy controls. All values determined in acromegalic patients were not within the confidence interval of the control group. Comparing the mean values of sulfate and thymidine incorporation in acromegalic and normal patients sulfate incorporation is enhanced by 57% and thymidine incorportion is enhanced by 75% in the posterior area in acromegaly.

In contrast to the posterior area sulfate and thymidine incorporation did not differ in the anterior free and the suprapremaxillary area of the septal cartilage in both groups.

DISCUSSION

In acromegaly one of the most salient clinical feature is the coarsening of the facial contours, which can be even more pronounced by the excessive enlargement of the nose.

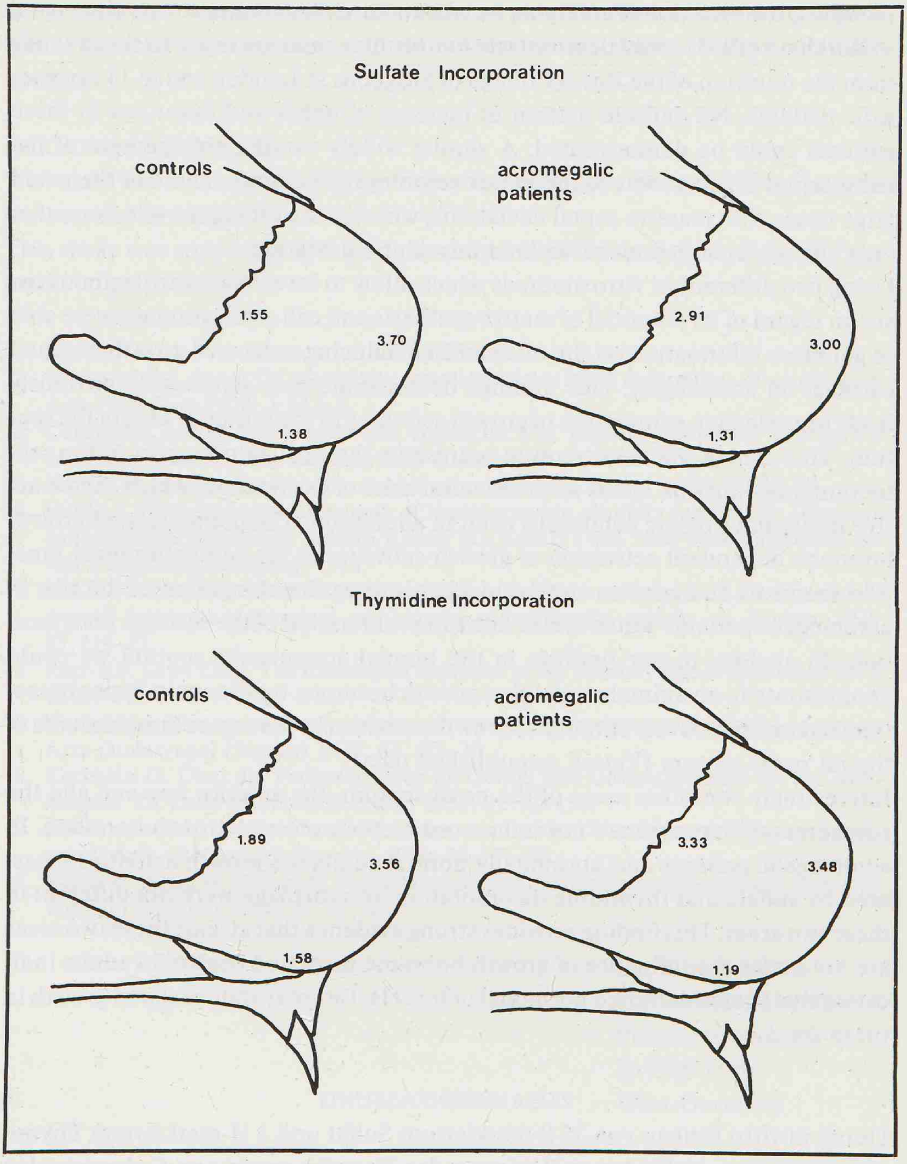

Figure 1. Growth activity measured by sulfate and thymidine incorporation in three areas of the human septal cartilage of 6 acromegalic patients and of 10 normal adult controls. The growth activity is expressed in 1000 counts/min/0.1 mg dry weight.

However, the variation of enlarging facial structures in acromegalic is rather wide as Korkhaus (1955) could demonstrate for the upper and lower jaw in seven skulls from the museum of the Royal College of Surgeons in London and in 13 acromegalic patients. No definite pattern in increase of upper and lower jaw in these patients could be demonstrated. A similar widely varying enlargement of the nasal septal cartilage was found in our acromegalic patients. Three of them had large noses with massive septal deviations, whereas the others showed normal or only slightly enlarged noses without any septal deviation.

Using two different in vitro methods which allow to investigate cartilaginous tissue in regard of its potential of matrix synthesis and cell replication we were able to get more information on the mechanisms inducing enhanced growth of septal cartilage in acromegaly. Our findings demonstrate that acromegaly obviously leads to a selective stimulation of growth activities in the posterior area of the septum. This area of the nasal septum represents the cartilaginous part of the septoethmoidal junction and is an enchondral zone of ossification, which can be active under physiologic conditions even in adulthood. The demonstrated growth hormone dependent activation of growth activities in the septoethmoidal junction seems to be based on similar mechanisms as the elongation of the ribs in acromegalic patients which is also due to a proliferation of the cartilage bone junction. In analogy to our findings in the human acromegalic septum we could demonstrate in an animal model that growth hormone treatment in hypophysectomized rats selectively stimulates growth activities in the septoethmoidal area of the rat nasal septum (Vetter, unpublished data).

Interestingly two other areas of the nasal septum, the anterior free end and the suprapremaxillary area are not influenced by the excess of growth hormone. In acromegalic patients and hormonally normal adults the growth activities measured by sulfate and thymidine incorporation into cartilage were not different in these two areas. This finding provides strong evidence that at least these two areas are not under the influence of growth hormone mediated control in adults indicating that yet unidentified hormonal or local factors may induce septal growth in these areas.

ZUSAMMENFASSUNG

Durch in vitro Einbau von 35 S-markiertum Sulfat und 3 H-markiertem Thymidin wurde in verschiedenen Regionen des Nasenknorpels von 6 akromegalen Patienten Wachstumsaktivität gemessen. Septumknorpel wurde während transnasaler Hypophysektomie gewonnen. Die Wachstumsaktivität in der septoethmoidalen Übergansregion war bei akromegalen Patienten signifikant gesteigert, während sich die Wachstumsaktivität in Septumspitze und supraprämaxillarer Region in beiden Gruppen nicht unterschieden. Unsere Ergebnisse weisen darauf hin, dass der Wachstumshormonüberschuss bei Akromegalen nur zur

Steigerung der Wachstumaktivität in der septoethmoidalen Übergangsregion führt, während Septumspitze und supraprämaxillare Region nicht beeinflusst werden.

ACKNOWLEDGEMENTS

We would like to thank Mrs. Pinzer for her technical assistance and Mrs. Haug for her secretarial help.

This study was supported by a grant from the Nordisc foundation, Gentoft, Denmark.

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