

## Altered $G_s$ and Adenylate Cyclase Activity in hGH-Secreting Pituitary Adenomas

Three investigators from Milan report two groups of human growth hormone (hGH)-secreting adenomas. The groups are differentiated by the adenylate cyclase activity in the cells grown in culture and the amount of hGH released in the basal, stimulated, and inhibited states.

The results in Group 1 are similar to those observed in normal rat pituitary cells. The results in Group 2 were completely different. The stimulatory effect of magnesium in Group 1 was significant but was even greater in Group 2. This hyperresponse, which occurred only with magnesium stimulation, could account for the high cyclic adenosine monophosphate (cAMP) levels observed in cultured cells because it was already appreciated at physiologic magnesium concentrations.

The authors noted that the altered regulation of adenylate

cyclase in tumors in Group 2 concerned only the guanine-stimulatory ( $G_s$ ) mechanism and not the guanine-inhibitory ( $G_i$ ) mechanism on cAMP activity. The authors postulate that tumors in Group 2 probably have a disturbance of stimulatory transmembrane signalling, which is located in the  $G_s$  protein, while adenylate cyclase activity and its resulting function (hGH release) resides in the  $G_s$  but not the  $G_i$  protein.

Since both secretion and growth of pituitary somatotropes are known to be under the control of cAMP, the authors suggest that a direct causal relationship between the alteration of guanine and the high secretory rate of these cells and their growth is possible.

Vallar L, Spada A, Giannattasio G. *Nature* 1987;330:566-568.

**Editor's comment**—Professor Henry R. Bourne, of the University of California at San Francisco, addressed this subject in the same issue of *Nature*. In his commentary

	Group 1	Group 2
hGH secretion/30 min/2 × 10 <sup>5</sup> cells	53.1 ± 12.6 ng	246.7 ± 78.3 ng
With GHRH	132 ± 0.0 ng	no increase
cAMP levels	2.2 ± 0.1 pmoles	49.5 ± 18.7 pmoles
With GHRH	17.6 ± 0.0 pmoles	no increase
Adenylate cyclase activity	12.64 ± 1.51*	102.49 ± 23.2*
With GHRH	40.60 ± 3.59*	125.38 ± 29.64*
With GTP	26.30 ± 5.25*	92.14 ± 14.71*
With Gpp(NH)p	21.45 ± 3.58*	67.17 ± 11.08*
With NAF	127.09 ± 16.94*	94.90 ± 15.74*
With Forskolin	55.61 ± 10.68*	263.53 ± 30.71*
With SRIF	10.53 ± 2.22*	68.96 ± 7.52*

\*pmol cAMP mg<sup>-1</sup> protein min<sup>-1</sup>

("G Proteins and cAMP: Discovery of a new oncogene in pituitary tumors?"), Bourne presented two possible explanations for the autonomous function of the tumors in Group 2. These are either a covalent modification or an activating mutation of G<sub>s</sub>. Bourne favors the

latter. He postulates that a somatic mutation in Group 2 tumors activates G<sub>s</sub> directly and cites precedent for a mutational replacement of residues in the nucleotide-binding pocket of normal cellular ras proteins. These mutations produce proteins with

reduced intrinsic capacity for hydrolyzing guanosine triphosphate (GTP) and, consequently, markedly diminished sensitivity to a GTP-ase-activating regulatory protein. Expression of these activated ras proteins causes malignant transformation of cells in vitro and contributes to oncogenesis in animals. Bourne also stated that cAMP can stimulate, inhibit, or have no effect on proliferation. It is already known that cAMP stimulates hGH secretion and proliferation of somatotropes. Other tropic hormones that use cAMP as a second messenger include the thyroid, adrenal, and sex glands. It is easy to imagine that tumors of these glands might result from the activation of mutations in G<sub>s</sub> protein or in other elements of the cAMP-signalling pathway.

Further speculation might be in order. Could the McCune-Albright syndrome, characterized by sexual precocity, cafe-au-lait spots, and polyostotic fibrous dysplasia, result from abnormal or mutated G<sub>s</sub>? We may know the answer in a few years.

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