# PHYSIOLOGICAL ROLE OF SOMATOSTATIN IN THE CONTROL OF GROWTH HORMONE AND THYROTROPIN SECRETION

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Summary: Intravenous injection of sheep antiserum to somatostatin in the rat not only increases basal plasma TSH levels but also potentiates TSH response following exposure to cold (5° C). Plasma levels of GH rise 2-3 fold during the first 3 h after injection of the antiserum, with a progressive decrease of the effect up to 10 h. Rhythmical change of serum GH levels during a 10-hour period of observation is not altered after antiserum injection. These data indicate that somatostatin plays a physiological role in the control of both TSH and GH secretion and suggest the involvement of GH-releasing hormone, in addition to somatostatin, in the GH release mechanism.

Somatostatin or GH release-inhibiting hormone (GH-RIH)[3] has been isolated from ovine (1) and porcine (2) hypothalami on the basis of its ability to inhibit GH release from anterior pituitary cells in culture. The tetradecapeptide is now well known to be a potent inhibitor of GH release in the rat under both *in vitro* (1, 4-6) and *in vivo* (6-8) conditions of basal and stiumulated hormone release. Administration of somatostatin inhibits also plasma GH levels in the dog (9), baboon (10) and human (11, 12). Somatostatin has also been found to inhibit the TRH-induced release of TSH both *in vivo* (6, 13) and *in vitro* (4, 6, 13) in the rat and *in vivo* (12, 14) in human beings.

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[3]Abbreviations: GH, growth hormone; TSH, thyrotropin; LHRH, luteinizing hormone-releasing hormone.

Although the presence of somatostatin in hypothalamic tissue (1, 2) and the demonstration of its inhibitory effect on GH and TSH release (3-14) after its exogenous administration both *in vitro* and *in vivo* strongly suggested a role of the peptide in the control of GH and TSH secretion, proof of its physiological role remained to be obtained. It was thus felt of interest to study the effect of injection of a somatostatin antiserum on plasma levels of both GH and TSH in the rat. In the event of a role of somatostatin in the physiological control of GH and TSH secretion, the antiserum should neutralize circulating somatostatin and lead to an increase of the plasma levels of these two hormones. The present data indicate clearly that somatostatin exerts a physiological role in the control of both GH and TSH secretion.

## MATERIALS AND METHODS

Male Sprague-Dawley rats (obtained from Candian Breeding Farms, St-Constant, Quebec) weighing 200-225 g on arrival were housed two per cage in a sound-attenuated and temperature-controlled room (24 ± 2°C) illuminated from 05:00 to 19:00 h. Purina rat chow and water were available ad libitum. After one week, a catheter (Venocath no: 18, Abbott) was inserted into the right superior vena cava of animals under ether anesthesia. Since any stressful procedure, including handling, inhibits GH secretion in the rat (15, 16), animals were handled three times a day for 10 days before beginning the experiment. One h before exposure to cold (5 ± 1°C), 1 ml of sheep anti-somatostatin serum developed as described (17) or normal sheep serum was injected through the catheter. 0.9 ml blood samples were withdrawn in heparinized seringes at the indicated time intervals. 0.9 ml of saline containing heparin was injected after each blood sampling to maintain blood volume. In the studies on plasma GH levels, 1 ml of sheep anti-

somatostatin or normal sheep serum was injected through the catheter at 9:00 h and 0.6 ml blood samples were withdrawn every 30 min during the following 10 h. After each blood sampling, red blood cells were resuspended in 0.6 ml of 0.9% saline and reinjected through the catheter.

Plasma was separated by centrifugation at 4000 xg for 10 min and kept at -20°C until TSH and GH assays. Plasma GH and TSH were measured by double-antibody radioimmunoassay (18, 19) using rat hormones (GH-I-2 and GH-RP-1, TSH-I-1 and TSH-RP-1) and rabbit anti serum (anti-GH-S-2 and anti-TSH-S-1) kindly provided by Dr. A.F. Parlow for the National Institute of Arthritis and Metabolic Diseases, Rat Pituitary Hormone Program. Purified goat anti-rabbit $\gamma$-globulins were a product of Endocrinolab Ltd., Quebec. Radioimmunoassay data were analysed using a program written in this laboratory and based on model II of Rodbard and Lewald (20). All results are expressed as mean $\pm$ S.E.M. Statistical significance was analysed according to the multiple-range test of Duncan-Kramer (21).

## RESULTS

Fig. 1 shows that administration of the somatostatin antiserum not only leads to a 100% increase of basal plasma TSH levels measured 60 min after its injection but also potentiates ($p < 0.05$) by about 80% the plasma TSH response measured 30 min after exposure to cold.

Since plasma GH levels in the rat show great variability (15, 22, 23), plasma GH levels were measured every 30 min for a period of 10 h. Left panels of Fig. 2 show representative patterns of plasma GH levels in control rats injected with 1 ml of normal sheep serum. All animals show episodic bursts of plasma GH with levels ranging from 5 to above 200 ng/ml. In animals injected

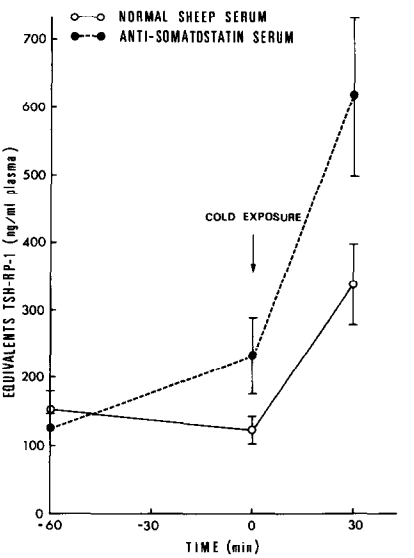


Fig. 1 Effect of sheep anti-somatostatin serum on the basal levels of plasma TSH and the response of the hormone to exposure to cold (5°C). 1.0 ml of sheep antiserum was injected through a catheter 1 hr before exposure to cold and plasma TSH measurements performed at the indicated time intervals.

with somatostatin antiserum (right panels), the pulsatile release of GH is maintained but the amplitude of the peaks is increased 2 to 3-fold. Fig. 3 illustrates more precisely the effect of the somatostatin antiserum on plasma GH levels in a group of ten freely-moving animals. The area under the first plasma GH-peak is increased 2 to 3-fold while the effect of the antibody, although still apparent, decreases progressively thereafter.

## DISCUSSION

The present data clearly show that administration of somatostatin antiserum leads to increased release of both GH and TSH, and thus indicate that somatostatin plays a physiological role in the control of both GH and TSH secretion.

The availability of highly specific antibodies to hormones offers an ideal means of assessing the physiological role of a parti-

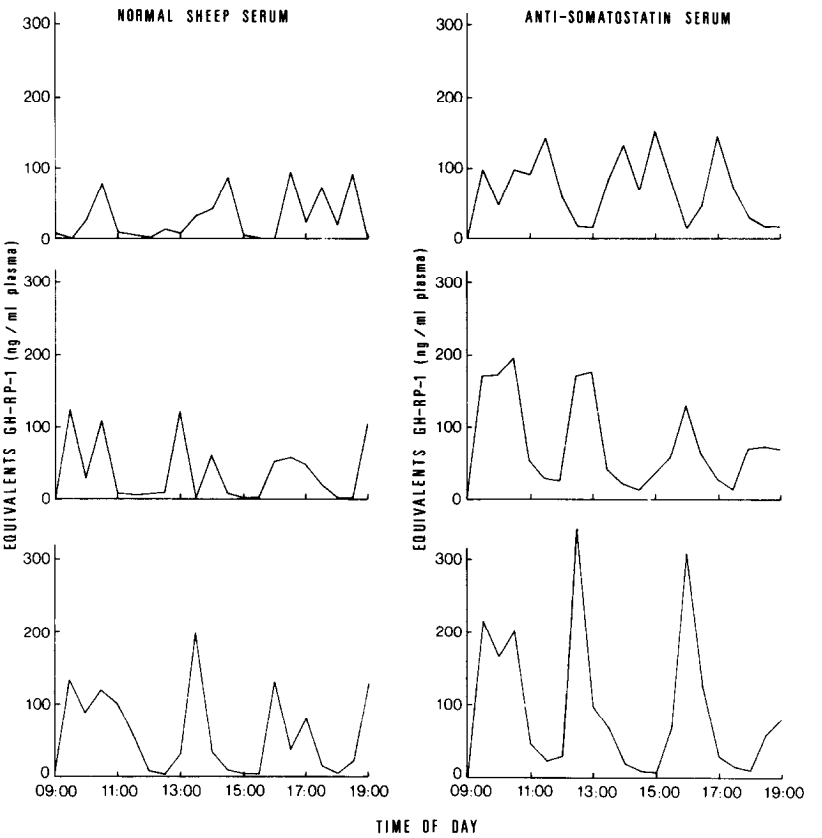


Fig. 2 Representative patterns of plasma GH in freely-moving animals who received 1.0 ml of normal sheep serum (left panels) or the same amount of sheep anti-somatostatin serum (right panels). Blood samplings were performed every 30 min.

cular hormone. In fact, injection of excess antibodies should neutralize the circulating hormone and lead to changes of the specific parameters under control. As examples, LHRH antiserum has been successfully used to study the role of this neurohormone in ovulation (24) and in the stimulation of LH release observed after *in vivo* administration of prostaglandins (25, 26).

In the rat, cold exposure leads to a rapid increase of plasma TSH levels (27, 28). The present findings that somatostatin antibody not only increases basal plasma TSH levels but also enhances very strongly its response to cold exposure suggest that the tetra-

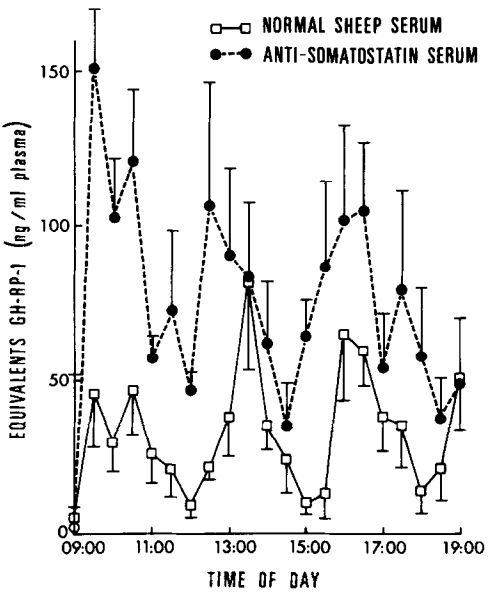


Fig. 3 Effect of sheep anti-somatostatin serum on plasma GH levels Data are presented as mean ± S.E.M. of 10 animals per group Control rats received an equivalent volume of normal sheep serum.

decapeptide plays a physiological role in the control of TSH secretion.

The data in Figs. 2 and 3, besides indicating a physiological role of somatostatin in the control of basal GH secretion, suggest that the episodic bursts of GH release occurring in the freely-moving rat are due to intermittent release of another regulator, probably GH-releasing hormone, from the hypothalamus.

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