insufficient anaerobic energy production during strenuous exercise, PGAM is the glycolytic enzyme with highest activity in normal human muscle (Table 1). Therefore, the small residual activity of the BB isoenzyme found in the patient was still approximately half that of phosphofructokinase, the rate-limiting enzyme of glycolysis. This incomplete block of the glycolytic pathway may explain the modest rise of venous lactate after ischemic exercise, the decreased but not absent formation of lactate by muscle extracts in anaerobic conditions, and the normal concentration of glycogen and glycolytic intermediates in muscle. The frequency of this enzyme defect remains to be determined, but muscle PGAM deficiency is now added to phosphorylase, phosphofructokinase, and carnitine palmityl transferase deficiencies in the differential diagnosis of human recurrent myoglobinuria.

Note added in proof: A genetic defect of the M subunit of lactate dehydrogenase has been recently reported in an 18-year-old man with recurrent myoglobinuria induced by intense exercise (*12*).

SALVATORE DIMAURO
ARMAND F. MIRANDA
SHAHNAZ KHAN, KEVIN GITLIN
H. Houston Merritt Clinical Research Center for Muscular Dystrophy and Related Diseases, Columbia University, College of Physicians and Surgeons, New York 10032
ROBERT FRIEDMAN
Department of Medicine, New York University, New York 10016

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Somatomedin-C Mediates Growth Hormone Negative Feedback by Effects on Both the Hypothalamus and the Pituitary

Abstract. *Somatomedin-C stimulates somatostatin release to a maximum of 390 percent of basal release during short-term (20-minute) incubation of rat hypothalamus. It has no effect on basal or stimulated growth hormone release from primary cultures of rat adenohypophyseal cells during a 4-hour incubation, but inhibits stimulated release by more than 90 percent after 24 hours. These findings suggest that somatomedin-C participates in the growth hormone negative feedback loop with an immediate effect on hypothalamic somatostatin and a delayed effect on the anterior pituitary.*

Homeostasis of the hypothalamic-pituitary–thyroid, –adrenal, and –gonadal axes is maintained largely by a feedback control. This control is exerted at multiple levels by the target gland hormones at the pituitary and hypothalamus and by the pituitary trophic hormones at the hypothalamus (*1*).

Central nervous system regulation of pituitary growth hormone (GH) secretion is mediated by the balance between a hypothalamic inhibiting factor—somatostatin—and an as yet uncharacterized releasing factor (*2*). We have previously demonstrated that GH acts at the hypothalamus to stimulate synthesis and release of somatostatin (*3*), suggesting a negative feedback control of this pituitary hormone at the hypothalamic level.

Although no distinct endocrine target organ for GH action is known, many of its peripheral effects, especially on tissue growth and anabolism, are mediated by the somatomedins (*4*). The somatomedins constitute a family of peptide hormones that includes insulin-like growth factors 1 and 2, with structures similar to that of proinsulin (*5*), and somatomedins SM-A (*6*), and SM-C (*7*). A feedback effect of these GH-dependent peptides on the regulation of GH might therefore be expected, but has not, to our knowledge, been described. To explore this possibility we have studied the effect of highly purified SM-C in vitro on the release of somatostatin by rat hypothalamus and of GH by dispersed rat adenohypophyseal cells in primary monolayer culture. The results indicate that SM-C stimulates hypothalamic somatostatin release during a 20-minute incubation in a dose-related manner and inhibits stimulated pituitary GH release after prolonged (24-hour) but not short-term (4-hour) exposure. These findings suggest that the acute SM-C feedback is exerted at the hypothalamic level and mediated by the release of somatostatin, whereas delayed effects occur at the anterior pituitary by direct inhibition of GH secretion.

Intact rat medial-basal hypothalamus (MBH) and septum and preoptic area (SPO) tissue blocks (*8*) were individually incubated in Krebs-Ringer bicarbonate buffer containing glucose (14 m*M*) and bacitracin (0.5 mg/ml) in an atmosphere of 95 percent O_2 : 5 percent CO_2. After a 60-minute equilibration period to achieve stable somatostatin release, a 20-minute basal incubation was performed in buffer alone (for MBH, 72 ± 5 pg of somatostatin, $N = 83$; for SPO, 129 ± 5 pg of somatostatin, $N = 104$). This was followed by a 20-minute incubation in buffer containing highly purified (*9*) SM-C (5 to 50 ng/ml) or control materials includ-

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Table 1. Effect of SM-C (25 ng/ml) on GH release by 4-day primary cultures of rat adenohypophyseal cells. Incubations were carried out for 4 and 24 hours under basal conditions or in the presence of dbcAMP (5×10^{-4} *M*) or GH-RP (0.8 μg/ml) (*17*). Results are expressed as mean ± standard error of the mean nanograms of rat GH per milliliter. Unpaired *t*-tests (degrees of freedom = $N_1 + N_2 - 2$) were used to analyze the data. N.S., not significant.

Incubation condition	Control		SM-C		*t*	*P*
	N	GH release (ng/ml)	*N*	GH release (ng/ml)		
		4-hour incubation				
Basal	18	183 ± 16	18	165 ± 9		N.S.
dbcAMP	17	481 ± 32*	18	444 ± 25*		N.S.
GH-RP	6	597 ± 72*	6	618 ± 73*		N.S.
		24-hour incubation				
Basal	18	139 ± 6	18	161 ± 10		N.S.
dbcAMP	16	1728 ± 135*	18	154 ± 6	12.4	< .001
GH-RP	6	1640 ± 121*	6	164 ± 7	12.2	< .001

*Significantly different from comparison basal incubation, $P < .001$.

ing bovine serum albumin (125 ng/ml), porcine proinsulin (25 ng/ml), porcine insulin (25 ng/ml), and mouse epidermal growth factor (25 ng/ml) (*10*). Media were removed after incubation, boiled for 10 minutes, and stored at −20°C until somatostatin was measured by radioimmunoassay (*11*).

Somatostatin release from MBH and SPO was stimulated in a dose-related manner by SM-C. Maximum somatostatin release from MBH of 279 ± 14 pg during 20 minutes was achieved with 35 ng of SM-C per milliliter. The 50 percent maximum stimulation (K_m) (*12*) occurred at 16 ± 2 ng of SM-C per milliliter (Fig. 1A). The maximum release of somatostatin from SPO was 205 ± 28 pg occurring in response to 25 ng of SM-C per milliliter, and a similar K_m to that for MBH (Fig. 1B). Previous reports have indicated that the K_m for binding of this SM-C preparation in radio-receptor studies is ± 10 ng/ml (*13*), similar to that in our studies, suggesting that the responses observed were produced by concentrations of SM-C within the physiologic range.

Specificity of the MBH and SPO somatostatin response to SM-C is suggested by the absence of effect of bovine serum albumin (representing a nonspecific protein control) and of insulin, proinsulin, and epidermal growth factor (other growth factors not directly stimulated by GH).

We have previously demonstrated that rat GH stimulates MBH somatostatin release in vitro at physiologic concentrations (10^{-10} *M* or 22 ng/ml) (*3*). This demonstration, together with the present data, suggests that there may be a dual mechanism for the negative feedback of GH on somatostatin release, one mediated directly by GH itself and the other through its peripheral effector, SM-C.

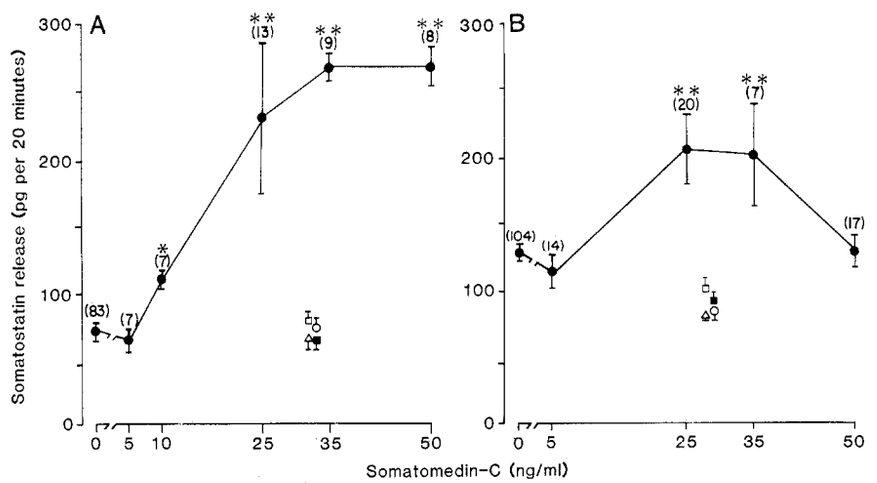

Fig. 1. Effects of highly purified SM-C on hypothalamic somatostatin release (●). (A) Dose-response curve for MBH somatostatin release. Results are expressed as means ± standard errors of the mean. The number of incubations is shown in parentheses. (B) Dose-response curve for SPO somatostatin release. Statistical comparisons were made against basal release by unpaired *t*-tests: * < .05; ** < .001. Control materials: □, bovine serum albumin ($N = 6$); ■, proinsulin ($N = 7$); △, insulin ($N = 7$); and ○, epidermal growth factor ($N = 8$).

The physiological relevance of this feedback effect of SM-C depends on its access in vivo to those hypothalamic nuclei or nerve terminals which participate in somatostatin secretion. While the permeability of the blood-brain barrier in this region to SM-C is not known, the presence of SM (assayed as sulfation factor) in cerebrospinal fluid has been reported (*14*), suggesting it may have access to the central nervous system.

The direct effect of SM-C on GH secretion was determined in 4-day primary cultures of dispersed rat adenohypophyseal cells (*15*) incubated for 4 or 24 hours in the presence or absence of the peptide at concentrations ranging from 5 to 125 ng/ml. Exposure of the cells to SM-C for 4 hours had no effect on basal GH release or that stimulated by dibutyryl adenosine 3′5′-cyclic monophosphate (dbcAMP) or by a GH-releasing peptide (GH-RP) derived from a pancreatic islet tumor (*16*), indicating the absence of acute SM-C effect at the anterior pituitary level. In contrast, incubation with SM-C (5 or 25 ng/ml) for 24 hours resulted in complete abolition of GH release stimulated by either agent (Table 1). Exposure of the cells to SM-C at similar concentrations for 24 hours had no effect on basal prolactin release (35 ± 1 versus 32 ± 1 ng/ml) or that stimulated by dbcAMP (44 ± 3 versus 47 ± 2 ng/ml) or thyrotropin-releasing hormone (60 ± 3 versus 56 ± 3 ng/ml), suggesting that SM-C action is directed at the somatotrophs. Specificity of the SM-C effect is indicated by the absence of an effect of proinsulin and epidermal growth factor on GH secretion. A small but reproducible inhibition by insulin of dbcAMP-stimulated GH release (± 35 percent) after 24 hours of incubation (1728 ± 135, $N = 16$, versus 1096 ± 55 ng/ml, $N = 6$, unpaired *t*-test, $t = 2.8$, $P < .02$) was much less marked than that seen with SM-C at the same concentration (154 ± 6, $N = 18$). This effect of insulin occurred at a concentration (25 ng/ml) greater than that normally required for insulin effect. The common effect of SM-C and insulin on GH release supports previous observations of shared activities between these peptides at some receptor sites (*4*).

Although the mechanism of SM-C inhibition of GH release remains to be determined, the delay in its onset suggests an alteration in cellular metabolism rather than a simple block in secretory process. Since the acute inhibitory effects of somatostatin on GH secretion are of limited duration (*17*), possibly due to down regulation of its receptors on the somatotroph, the delayed effect of SM-C

would complement those of somatostatin, thereby providing the means for both short- and long-term inhibition of GH secretion.

We have described the in vitro stimulatory effects of SM-C on hypothalamic somatostatin release and inhibitory effects on pituitary GH secretion. Together with our previous report that GH directly stimulates hypothalamic somatostatin accumulation and release, our studies provide a more complete picture of pituitary GH regulation: GH promotes synthesis and release of the somatomedins, including SM-C. Both SM-C and GH act rapidly at the level of the hypothalamus (primarily the MBH) to stimulate somatostatin release, thereby inhibiting further GH secretion. The possibility of a simultaneous effect of SM-C or GH on hypothalamic GH-releasing factor cannot as yet be determined. More prolonged exposure to SM-C causes direct inhibition of GH release by the pituitary and could account for some of the impaired GH responses seen in patients with GH-secreting pituitary tumors.

MICHAEL BERELOWITZ
MARTA SZABO
LAWRENCE A. FROHMAN
SUSAN FIRESTONE
LILY CHU
Division of Endocrinology and Metabolism, Michael Reese Hospital and University of Chicago, Chicago, Illinois 60616
RAYMOND L. HINTZ
Department of Pediatrics, Stanford University, Palo Alto, California 94305

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9. Highly purified SM-C was prepared by the method of J. M. Horner, F. Liu, and R. L. Hintz [*J. Clin. Endocrinol. Metab.* **47**, 1287 (1978)] and shown to be homogenous by gel electrophoresis and thin-layer isoelectric focusing. This preparation is identical to IGF-1 and the SM-C preparation of J. J. Van Wyk in several different radioligand assays [*ibid.* **50**, 405 (1980)].
10. Bovine serum albumin provided a control for nonspecific protein effects; proinsulin has a structure similar to that of IGF-1 and -2 (though possibly not to that of SM-C); insulin shares many biologic effects with the somatomedins (though of a lesser potency); and epidermal growth factor represents a non-GH-dependent factor with anabolic and trophic effects on tissue.
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Infant Carrying by Male Chacma Baboons

Abstract. *Male chacma baboons,* Papio ursinus, *carry their offspring during confrontations with higher ranking immigrant males, who are a threat to the infants' lives. The infants sometimes initiate these confrontations by approaching and provoking immigrant males when protective males are close by. Mothers rarely interfere during these interactions.*

A frequently observed but poorly understood feature of savanna baboon (*Papio* spp.) societies is that an adult male sometimes carries an infant during interactions with another male (*1–3*). Explanations of this behavior, originally termed agonistic buffering (*4*), are that by carrying an infant a male reduces his probability of being attacked (*1–3*) or increases his probability of gaining access to an estrous female (*2*) or food (*2, 3*). The assumption is that the carrying male gains an advantage by exploiting an infant who is probably the opponent's offspring (*2*). In this report we present the opposite interpretation: that the infant is probably the carrying male's offspring and that carrying protects the infant from potentially infanticidal immigrants. Thus, we identify infant carrying as a form of paternal care. This interpretation provides a new link in the understanding of paternal investment (*5*) and infanticide (*6*) in polygamous primate groups.

During a 3-year study of chacma baboons (*Papio ursinus*) in the Moremi Wildlife Reserve, Botswana, we saw adult males kill only two infants and wound two others (*7*). Three of the attackers were immigrant males; the fourth was unidentified. [Male baboons have also attacked infants at other study sites (*3, 6, 8*).] Infanticide may be infrequent because resident troop members protect infants from immigrant males (*6, 9*).

Our analysis of infant carrying by males focuses on the infant's paternity. Males compete to mate with females, and dominant males sire most of the infants in a troop (*10*). This conclusion is based on field observations of mating patterns 3 days before the female's estrous swelling begins deflating ("D − 3"). Studies of reproduction in captive baboons suggest that matings on D − 3 have the highest probability of resulting in conception (*11*). Another factor influencing paternity is that males leave one troop and join another at least once in their lifetimes (*9*): a male joining a troop after an infant's conception cannot be the father.

The effect of infant death on a mother's reproductive behavior (*12*) is another important aspect in this analysis. Baboon infants are weaned at about 12 months of age, and mothers conceive 18 months (532 ± 23 days, N = 13) after the birth of an infant who survives to weaning. However, if an infant dies before weaning, the mother becomes sexually receptive after a few weeks and conceives 4 months (134 ± 19 days, N = 8) after the death. Thus, by killing an unweaned infant, a male enhances his opportunity to impregnate the mother earlier than he could otherwise (*6, 13*).

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