activity of multiple brain areas in individual female rats. We cannot, at present, relate a specific brain area to a specific behavioral or physiological consequence of copulatory stimulation. We speculate that the MPOA acts as a receiving area for copulatory information provided by cervical stimulation during mating (*21*). The brief stimulation from each intromission may be integrated in this brain site, even when the intromissions are widely spaced (*22*). At a later time (*23*) the MPOA is inhibited to allow the progestationally relevant nocturnal surges of prolactin to occur (*24*).

T. O. ALLEN
N. T. ADLER

Department of Psychology, University of Pennsylvania, Philadelphia 19104

J. H. GREENBERG
M. REIVICH

Cerebrovascular Research Center, Department of Neurology, Hospital of the University of Pennsylvania, Philadelphia 19104

References and Notes

1. R. E. Kuehn and F. A. Beach, *Behaviour* **21**, 282 (1963); C. Diakow, *J. Comp. Physiol. Psychol.* **88**, 704 (1975).
2. J. R. Wilson, N. T. Adler, B. LeBoef, *Proc. Natl. Acad. Sci. U.S.A.* **53**, 1392 (1965); M. E. Freeman, M. S. Smith, S. J. Nazian, J. D. Neill, *Endocrinology* **94**, 875 (1974); R. L. Butcher, W. E. Collins, N. W. Fugo, *ibid.*, p. 1704.
3. R. L. Moss and K. J. Cooper, *Endocrinology* **92**, 1748 (1973).
4. M. Matthews and N. T. Adler, *J. Comp. Physiol. Psychol.* **91**, 727 (1977).
5. B. R. Komisaruk, in *Reproductive Behavior*, E. Montagna and W. A. Sadler, Eds. (Plenum, New York, 1974), pp. 97–129.
6. M. S. Smith, B. K. McLean, J. D. Neill, *Endocrinology* **98**, 1370 (1976); C. Diakow, *Am. Zool.* **10**, 486 (1970).
7. D. W. Lincoln, *J. Endocrinol.* **43**, 683 (1969); C. A. Barraclough and B. A. Cross, *ibid.* **26**, 339 (1963); G. Margherita, D. Albritton, R. MacInnes, R. Hayward, R. A. Gorski, *Exp. Neurol.* **13**, 96 (1965); B. A. Cross and I. A. Silver, *J. Endocrinol.* **31**, 251 (1965); V. D. Ramirez, B. R. Komisaruk, D. I. Whitmoyer, C. H. Sawyer, *Am. J. Physiol.* **212**, 1376 (1967); C. W. Malsbury, D. B. Kelly, D. W. Pfaff, *Proc. 4th Int. Cong. Endocrinol.* (1972), p. 205; M. Kawakami and K. Kubo, *Neuroendocrinology* **7**, 65 (1971); C. A. Blake and C. H. Sawyer, *ibid.* **10**, 358 (1972).
8. J. B. Hornby and J. D. Rose, *Exp. Neurol.* **51**, 363 (1976).
9. B. Powers and E. S. Valenstein, *Science* **175**, 1003 (1972); D. M. Nance, J. E. Shryne, R. A. Gorski, *Horm. Behav.* **5**, 73 (1974); F. A. Beach, *Psychosomat. Med.* **6**, 40 (1944); H. Carrer, G. Asch, C. Aron, *Neuroendocrinology* **13**, 129 (1973/1974); H. F. Carrer, *J. Comp. Physiol. Psychol.* **92**, 877 (1978); D. T. Modianos and D. W. Pfaff, *Brain Res.* **106**, 47 (1976); J. G. Herndon, *Physiol. Behav.* **17**, 143 (1976); D. T. Modianos, J. C. Hitt, J. Flexman, *Behav. Biol.* **10**, 75 (1974); T. Law and W. Meagher, *Science* **128**, 1626 (1958); J. Singer, *J. Comp. Physiol. Psychol.* **66**, 738 (1968).
10. J. W. Everett and D. L. Quinn, *Endocrinology* **78**, 141 (1966); J. E. Beach, L. Tyrey, J. W. Everett, *ibid.* **103**, 2247 (1978); M. E. Freeman and J. A. Banks, *ibid.* **106**, 608 (1980).
11. L. Sokoloff, M. Reivich, C. Kennedy, M. H. DesRosiers, C. S. Patlak, K. D. Pettigrew, O. Sakurada, M. Shinohara, *J. Neurochem.* **28**, 897 (1977).
12. Gonadal hormones affect both the peripheral and the central mechanisms for processing sensory input [B. R. Komisaruk, N. T. Adler, J. Hutchison, *Science* **178**, 1295 (1972); B. R. Komisaruk, P. G. McDonald, D. I. Whitmoyer, C. H. Sawyer, *Exp. Neurol.* **19**, 494 (1967)].
13. For each of two consecutive weeks, estradiol cypionate (0.05 mg per 0.1 ml of oil) was injected intramuscularly two times, 48 hours apart, and was followed 24 hours later by progesterone (0.5 mg per 0.1 ml of oil).
14. One week before the experiment the rats were anesthetized with Chloropent (0.3 ml per 100 g), and one end of the catheter (Dow Silastic tubing; inner diameter, 0.020 inch; outer diameter, 0.037 inch) was inserted into the right jugular vein. The other end was capped, threaded under the skin behind the ear, and anchored to the top of the skull with dental cement. To maintain patency, catheters were filled with a 33 percent solution of polyvinylpyrrolidone in heparinized saline fortified with gentamicin.
15. The vibroengraving tool (Ideal Industries, Sycamore, Ill.) was adjusted to its slowest speed. The stimulation was not painful because (i) in preliminary work, when the vibrator was applied to the cervix of female rats, no tissue damage of the cervix or vagina was found; (ii) the animals gave no overt signs of distress during the stimulation; and (iii) vaginocervical stimulation is analgesic, not nocioceptive [E. L. Ross, B. R. Komisaruk, D. O'Donnell, *J. Comp. Physiol. Psychol.* **93**, 330 (1979)].
16. With this schedule we tried to both mimic the intermittent stimulation provided by a male rat during coitus and produce a sufficiently high level of stimulation to optimize the 2-DG method. In a preliminary study we tested 19 female rats. Six of the nine stimulated females produced deciduomata; none of the ten unstimulated animals responded. Formation of deciduomata requires not only that the stimulation reach the brain but that the anterior pituitary and ovary release sufficient prolactin and progesterone, respectively, to affect the uterus.
17. At this time the brains of two of the animals in each group were perfused in situ with 3.3 percent buffered Formalin. Such perfusion does not affect the retention of the isotope [P. J. Hand, in *Methods in Contemporary Neuroanatomy: The Tracing of Central Nervous Pathways*, L. Heimer and M. Rolands, Eds. (Plenum, New York, in press)]. The brains of all eight rats were removed and frozen in Freon (−45°C), stored at −70°C, and cut into 20 sections on a cryostat at −16° to −18°C. The sections were exposed to x-ray film (Kodak SB5) for 10 days along with a set of six methylmethacrylate standards with known concentrations of ^{14}C.
18. J. F. R. Koenig and R. A. Klippel, *The Rat Brain* (Williams & Wilkins, Baltimore, 1963); M. Palkovits and D. M. Jacobowitz, *J. Comp. Neurol.* **157**, 29 (1974).
19. W. J. Schwartz and H. Gainer, *Science* **197**, 1089 (1977).
20. Telencephalon: frontal, pyriform, cingulate, parietal, and auditory cortices, hippocampus (Ammon's horn and dentate gyrus), nucleus accumbens, corticomedial and basolateral amygdala, lateral septum, caudate/putamen. Diencephalon: lateral and ventral thalamus, lateral and medial geniculate nuclei, lateral hypothalamus, suprachiasmatic nucleus, paraventricular nucleus, dorsomedial nucleus, ventromedial nucleus, posterior nucleus, mammillary bodies. Mesencephalon: inferior and superior colliculi, substantia nigra, central gray, red nucleus, interpeduncular nucleus. Metencephalon: cerebellar cortex. Myelencephalon: vestibular and cochlear nuclei, superior and inferior olivary nuclei, nucleus reticularis gigantocellularis.
21. C. A. Blake and C. H. Sawyer, *Neuroendocrinology* **10**, 358 (1972).
22. S. Edmonds, S. R. Zoloth, N. T. Adler, *Physiol. Behav.* **8**, 161 (1972).
23. M. S. Smith and J. D. Neill, *Endocrinology* **98**, 324 (1976).
24. M. E. Freeman and J. A. Banks, *ibid.* **106**, 668 (1980); C. L. Bethea and J. D. Neill, *ibid.* **107**, 1 (1980).
25. We thank H. Bradford and A. Sylvestro for their valuable technical assistance. Supported by NIMH grant I T32 MH 15092 (T.O.A.), PHS program project grant NS 10939-08 (J.H.G. and M.R.), and NIH grant HD 04522 (N.T.A.). These data were reported in preliminary form in *Soc. Neurosci. Abstr.* **4**, 339 (1978).
* Correspondence should be addressed to T.O.A.

28 July 1980; revised 18 November 1980

Paradoxical Elevation of Growth Hormone by Intraventricular Somatostatin: Possible Ultrashort-Loop Feedback

Abstract. *Somatostatin, the growth hormone–inhibiting factor, when microinjected into the third ventricle of the rat brain, paradoxically induced the release of growth hormone. A pituitary site of action having been ruled out, this result supports the concept that exogenous somatostatin within the hypothalamus acts either to suppress the release of somatostatin from somatostatin-containing neurons, possibly via an ultrashort-loop feedback mechanism, or to augment release of hypothalamic growth hormone–releasing factor, thereby inducing a release of growth hormone. Injection of somatostatin into the third ventricle also decreased plasma concentrations of luteinizing hormone, follicle-stimulating hormone, and thyroid-stimulating hormone, probably by inhibiting the release of luteinizing hormone–releasing factor and thyrotropin-releasing factor.*

The somatotropin release-inhibiting factor (SRIF) was discovered in partially purified hypothalamic extracts by Krulich *et al.* (*1*) on the basis of its ability to inhibit growth hormone (GH) secretion by the pituitary in vitro. This tetradecapeptide, isolated and characterized by Brazeau *et al.* (*2*) and renamed somatostatin, inhibits GH release both in vivo and in vitro (*2, 3*).

Not only does SRIF inhibit GH release, but it depresses several components of the central nervous system (*4*). For instance, the microiontophoretic application of SRIF to certain hypothalamic and extrahypothalamic structures depresses neuronal firing activity (*5*). We examined the participation of centrally administered SRIF in the regulation of its own hypothalamic secretion and in that of other hypothalamic peptides. This was accomplished by monitoring the effects of central and systemic SRIF treatment on the secretion of GH, luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), and prolactin (PRL), all of which are pituitary hormones under the control of hypothalamic releasing or inhibiting factors. In addition, we compared in rats the responses obtained with SRIF to those obtained following injection of the decapeptide luteinizing hormone–releasing factor (LHRH).

0036-8075/81/0306-1072$00.50/0

Table 1. Effect of the intraventricular administration of SRIF or saline on the plasma concentrations of LH, FSH, and TSH. Hormone values (means ± standard errors) are shown at time zero (immediately before intraventricular injection) and at 15, 30, and 60 minutes after the injection; N is the number of animals per group. Levels of significance were determined by the paired-sample t-test comparing hormone values before and after a particular treatment. For TSH measurements, five animals were used for each time interval within each treatment group.

Treatment	N	LH (ng/ml)				FSH (ng/ml)				TSH (ng/ml)			
		0	15	30	60	0	15	30	60	0	15	30	60
Saline	11	20.4 ± 1.2	20.4 ± 2.5	17.1 ± 1.9	19.1 ± 3.4	1429 ± 105	1419 ± 124	1391 ± 101	1246 ± 77	326.4 ± 42.2	295.7 ± 54.5	311.3 ± 34.3	333.1 ± 63.4
SRIF													
5 μg	10	22.0 ± 0.3	17.1 ± 2.4*	18.8 ± 2.3	19.6 ± 2.3	1556 ± 117	1283 ± 95‡	1396 ± 77*	1423 ± 94	375.7 ± 74.6	200.7 ± 47.0†	204.8 ± 34.2*	232.2 ± 53.6
1 μg	5	25.6 ± 4.5	13.7 ± 2.2‡	26.4 ± 3.4	24.3 ± 3.4	1709 ± 150	1606 ± 158	1605 ± 135	1659 ± 164	361.4 ± 89.6	141.9 ± 7.5*	154.9 ± 12.3*	

*$P < .05$. †$P < .025$. ‡$P < .01$.

Adult female rats that had been ovariectomized 4 weeks earlier had cannulas implanted in the third ventricle of the brain for injection of test substances, and Silastic cannulas implanted in the right external jugular vein to facilitate blood sampling in conscious animals. Peptides prepared in sterile saline or saline alone were injected into the ventricle in a volume of 4 μl over 60 seconds. Doses were 1 or 5 μg of synthetic SRIF or 1 μg of synthetic LHRH (*6*). Heparinized blood samples of 250 to 300 μl were withdrawn just before microinjection and at 15, 30, 60, 120 and, in some instances, 240 minutes after microinjection. Hormone values were measured by radioimmunoassay (*7*). Statistical significance within a treatment group was determined by the paired t-test (*8*). Significance between the means of treatment groups was determined by analysis of variance, the Student-Newman-Keuls test, and Student's t-test (*8*).

Injection of 5 μg of SRIF into the third ventricle induced two- to threefold increments in plasma GH at 15 ($P < .05$), 30 ($P < .0025$), and 60 ($P < .01$) minutes after injection (Fig. 1A). Peak values, reached at 30 minutes, also were significantly greater than corresponding values in animals receiving saline ($P < .005$) or LHRH ($P < .05$). Growth hormone concentrations were no longer significantly elevated at 120 and 240 minutes. To determine the latency of the rise in GH, we obtained blood samples 5 minutes after SRIF injection into the third ventricle in three rats; GH had already increased slightly in two animals and considerably in the third (*9*).

Injection of 1 μg of SRIF induced a sixfold increase in GH at 15 minutes ($P < .05$); values at 30 minutes were still double the values obtained before injection ($P < .025$) (Fig. 1A). The effects of this dose lasted a shorter time than those of the 5-μg dose. Values peaked at 15 minutes and were significantly greater than those for animals receiving saline ($P < .005$) or LHRH ($P < .05$). By 60 minutes GH had fallen below the baseline value. Administration of saline into the third ventricle did not affect GH levels (Fig. 1B). Furthermore, LHRH injected intraventricularly failed to alter GH values significantly at the times studied (Fig. 1B).

The effects of central administration of SRIF versus those produced by systemic administration were compared in ovariectomized rats prepared only with jugular cannulas. Intravenous injection of 5 μg of SRIF or saline diluent did not significantly change basal GH, TSH, FSH, or LH concentrations (not shown).

In an additional experiment, administration of SRIF (1 μg) into the third ventricle was followed 5 minutes later by an intravenous injection of SRIF (100 μg). In control animals, injection of SRIF into the third ventricle was followed by saline given intravenously. The clear increment in GH ($P < .05$) after the central injection of SRIF was completely blocked by systemic administration of SRIF ($P < .025$), and values were even lower than baseline ($P < .05$) after 15 minutes (Fig. 1C). By 30 minutes, GH values had rebounded, but to levels significantly lower ($P < .05$) than those in the group that received the SRIF intraventricularly and the saline intravenously.

Intraventricularly administered SRIF reduced plasma concentrations of LH, FSH, and TSH. Both the 1- and 5-μg doses of SRIF significantly ($P < .01$ and $P < .05$, respectively) decreased LH values 15 minutes after injection (Table 1). Only the 5-μg dose of SRIF caused a significant decrease in FSH 15 and 30 minutes after injection ($P < .01$ and $P < .05$, respectively); saline-injected rats showed no changes in LH or FSH. Saline injected into the third ventricle had no effect on plasma TSH, but intra-

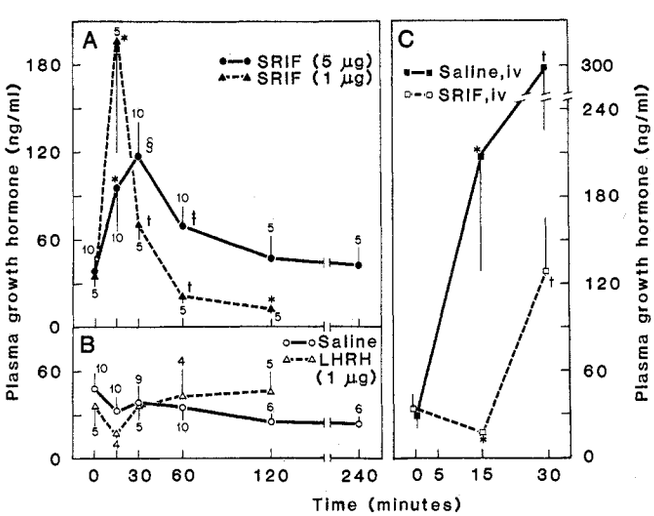

Fig. 1. (A) Effect on plasma GH of injection of 1 or 5 μg of SRIF into the third ventricle in ovariectomized rats. (B) Effect on plasma GH of saline or LHRH (1 μg) injection into the third ventricle. Points represent the means of hormone values and vertical bars represent the standard errors. Serial blood samples were taken at zero (0) time (immediately before intraventricular administration) and 15, 30, 60, 120, and in some instances, 240 minutes after microinjection. The sample size at each point is indicated above or below the standard error bar. Levels of significance were determined by the paired-sample t-test, comparing hormone values before and after a particular treatment (*$P < .05$, †$P < .025$, ‡$P < .01$, and §$P < .0025$). (C) Five minutes after 1 μg of SRIF was microinjected into the third ventricle, six rats received a bolus of 100 μg of SRIF intravenously (*iv*) and five rats received a corresponding volume of saline intravenously. Blood samples were taken at zero time and 15 and 30 minutes after the intraventricular injection to determine plasma GH levels. Levels of significance are denoted as above.

ventricular administration of 1 or 5 μg of SRIF significantly decreased TSH values at 15 and 30 minutes (Table 1). Neither saline nor SRIF produced a significant variation in plasma concentrations of PRL during the intervals examined (not shown).

Injection of LHRH into the third ventricle drastically increases plasma levels of its target pituitary hormone, LH (*10*). This effect has been attributed to the uptake of the peptide by the hypothalamus and its subsequent transport to the pituitary by the hypophysial portal system of veins (*10*). Thyrotropin-releasing factor (TRH) administered intraventricularly similarly stimulates TSH release from the pituitary (*11*). These findings suggest that injection of SRIF into the third ventricle should suppress GH levels, since SRIF suppresses GH release from dispersed pituitary cell incubations, pituitary perfusions and perifusions, and after systemic administration (*2, 3, 12*).

Instead of a suppression, we have found a paradoxical elevation of plasma GH after injection of SRIF into the third ventricle. Regions of the hypothalamus that contain SRIF also contain neurons with branching axon collaterals, one of which terminates on the portal vessels and the other in the tuberoinfundibular area (*13*). The phenomenon of recurrent inhibition within the tuberoinfundibular area, whereby axon collaterals may return to and synapse at their cell bodies of origin in order to inhibit their firing has been described (*14*). Such a recurrent neuronal circuitry could provide the pathway for an ultrashort-loop feedback mechanism for SRIF, a concept originally formulated for neurohormones by Martini (*15*). The uptake of exogenous SRIF by the hypothalamus may provide high local concentrations of the peptide in the vicinity of the cell bodies of the SRIF neurons in the region adjacent to the third ventricle (*16*); this could suppress the release of endogenous SRIF, thereby removing somatostatin-activated inhibition of pituitary GH release. Increased plasma GH would result.

Another mechanism by which SRIF might induce GH release by the pituitary would be by stimulation of the release of growth hormone–releasing factor (GHRF) from neurons in the hypothalamus. SRIF in the vicinity of these neurons might augment rather than inhibit GHRF release. Since SRIF generally has an inhibitory action (*4*), it might depress the firing of inhibitory interneurons that synapse with the GHRF elements. This would remove the inhibition and lead to release of GHRF, which then would stimulate the release of GH. Our results do not distinguish between these two possibilities nor do they exclude the possibility of an indirect effect on SRIF neurons via neurotransmitters or other hypothalamic peptides.

The 1-μg dose of SRIF was more effective than the 5-μg dose in producing a peak elevation of GH. The smaller peak following the larger dose of SRIF could be due to a certain amount of exogenous SRIF reaching the pituitary gland after uptake by the portal vessels, which then would suppress GH release to some extent. The smaller dose, however, would have less direct inhibitory action on the pituitary, and thereby the removal of endogenous hypothalamic SRIF would lead to a greater elevation of GH. The longer period of elevation of GH after the larger dose is probably caused by an extended suppression of endogenous release.

Evidence of a similar self-regulating somatostatin system has been obtained in the D cells of the pancreas, where injection of SRIF analogs resulted in decreased circulating SRIF immunoreactivity (*17*).

The fact that intravenous administration of 100 μg of SRIF blocked the stimulatory action of the intraventricularly administered peptide is further evidence that the GH release induced by somatostatin is centrally mediated and that, in agreement with previous reports (*2, 3, 12*), SRIF, when delivered to the anterior pituitary via systemic injections or in vitro, has only inhibitory effects on GH release.

Because centrally applied SRIF decreased LH and FSH at 15 minutes, and because SRIF does not act on the pituitary to affect gonadotropin secretion (*2, 3, 18*), a hypothalamic site of action for SRIF to block neuronal LHRH secretion is indicated. It is also possible that the decrease of basal TSH levels after central SRIF injection is the result of a SRIF-induced inhibition of hypothalamic TRH secretion (*19*).

Since the completion of these experiments, we have become aware of a report (*20*) in which a similar elevation of GH followed injection of SRIF into the lateral ventricle of urethane-anesthetized male rats. In another study (*21*), SRIF administered by the same route into anesthetized male rats that had been primed with pharmacological doses of estrogen had no effect on plasma GH. A clarification of these conflicting results is provided by our use of conscious animals and administration of SRIF closer to its presumed site of action in the hypothalamus.

Our results provide evidence for the existence of a hypothalamic mechanism by which neuronal SRIF may inhibit its own secretion (possibly by an ultrashort-loop feedback system), as well as that of other hypothalamic-releasing hormones, and may prompt the release of GHRF.

MICHAEL D. LUMPKIN
ANDRES NEGRO-VILAR
SAMUEL M. MCCANN

Department of Physiology, University of Texas Health Science Center at Dallas, Dallas 75235

References and Notes

1. L. Krulich, A. P. S. Dhariwal, S. M. McCann, *Endocrinology* **83**, 783 (1968); L. Krulich, P. Illner, C. P. Fawcett, M. Quijada, S. M. McCann, in *Growth and Growth Hormone*, A. Pecile and E. Muller, Eds. (Excerpta Medica, Amsterdam, 1972), p. 316.
2. P. Brazeau, W. Vale, R. Burgus, N. Ling, M. Butcher, J. Rivier, R. Guillemin, *Science* **179**, 77 (1973).
3. R. Hall, M. Snow, M. Scanlon, B. Mora, A. Gomez-Pan, *Metabolism* **27**, 1257 (1978).
4. S. M. McCann, L. Krulich, A. Negro-Vilar, S. R. Ojeda, E. Vijayan, in *Regulation and Function of Neural Peptides*, M. Trabucchi, Ed. (Raven, New York, in press).
5. L. P. Renaud, J. B. Martin, P. Brazeau, *Nature (London)* **255**, 233 (1975).
6. Synthetic SRIF and LHRH were obtained from Peninsula Laboratories, San Carlos, Calif.
7. Kits from the National Institute of Arthritis, Metabolism, and Digestive Diseases were used for measurements of GH, FSH, TSH, and PRL; LH was measured by the method of G. D. Niswender, A. R. Midgley, S. E. Monroe, and L. E. Reichert [*Proc. Soc. Exp. Biol. Med.* **128**, 807 (1968)] and expressed in terms of the NIH-LH-S1 reference preparation. Antiovine LH serum was provided by G. D. Niswender, and purified ovine LH for radioiodination was provided by L. E. Reichert.
8. J. H. Zar, *Biostatistical Analysis* (Prentice-Hall, Englewood Cliffs, N.J., 1974), pp. 121–124 and 133–135.
9. Plasma GH concentrations (nanograms per milliliter) after 5 μg of SRIF were injected into the third ventricle.

Rat	Minutes				
	0	5	15	30	60
I-2	18.1	20.7	42.1	57.3	28.2
I-3	23.2	24.5	26.0	87.8	24.7
I-9	46.6	78.4	222.6	157.3	75.7

10. N. Ben-Jonathan, R. S. Mical, J. C. Porter, *Endocrinology* **95**, 18 (1974); F. I. Weiner, J. Terkel, C. A. Blake, A. V. Schally, C. H. Sawyer, *Neuroendocrinology* **10**, 261 (1972).
11. C. Oliver, N. Ben-Jonathan, R. S. Mical, J. C. Porter, *Endocrinology* **97**, 1138 (1975).
12. H. E. Carlson, I. K. Mariz, W. H. Daughaday, *ibid.* **94**, 1709 (1974); M. E. Stachura, *ibid.* **99**, 678 (1976); P. Brazeau, J. Rivier, W. Vale, R. Guillemin, *ibid.* **94**, 184 (1974).
13. J. B. Martin, S. Reichlin, G. M. Brown, *Clinical Neuroendocrinology* (Davis, Philadelphia, 1977), pp. 147–177.
14. L. P. Renaud, in *The Hypothalamus*, S. Reichlin, R. J. Baldessarini, J. B. Martin, Eds. (Raven, New York, 1978), p. 269.
15. M. Hyyppa, M. Motta, L. Martini, *Neuroendocrinology* **7**, 227 (1971).
16. R. Elde and J. Parsons, *Am. J. Anat.* **144**, 541 (1975).
17. E. Ipp, J. Rivier, R. E. Dobbs, M. Brown, W. Vale, R. H. Unger, *Endocrinology* **104**, 1270 (1979).
18. W. Vale, P. Brazeau, C. Rivier, J. Rivier, R. Guillemin, in *Advances in Human Growth Hormone Research*, S. Raiti, Ed. (Department of Health, Education, and Welfare, Washington, D.C., 1973), p. 159.
19. Y. Hirooka, C. Hollander, S. Suzuki, P. Ferdinand, S.-I. Juan, *Proc. Natl. Acad. Sci. U.S.A.* **75**, 4509 (1978).
20. H. Abe, Y. Kato, Y. Iwasaki, K. Chihara, H. Imura, *Proc. Soc. Exp. Biol. Med.* **159**, 346 (1978).
21. K. Maeda and L. Frohman, *Endocrinology* **103**, 1903 (1978).
22. This work supported by grants HD-09988, HD-07062, and AM-10073 from the National Institutes of Health.

9 September 1980