apparent acute alterations in either endocrine or immune functions (*14*). The same is true of other species, although the time period when the thymus can be removed without altering function varies among species (*15*). Such data support the concept that there is interdependence of the immune and endocrine systems early in ontogeny only when critically important steps in the development and programming of neuroendocrine functions are occurring (*16*).

Our findings provide evidence linking neuroendocrine and immune functions, and suggest a new area of research with implications to the understanding and control of reproductive function. Since we show that synthetic thymosin β_4 can release LRF it should be possible to examine the mechanism by which LRF secretion is stimulated and to characterize the role of thymosin β_4 (and possibly other thymic peptides) within the reproductive system. Furthermore, the potential clinical usefulness of thymosin β_4 in eliciting LRF release in women in whom endogenous LRF secretion is diminished for the purpose of inducing ovulation is obvious as is the possible effectiveness of analogs of this peptide for the same (or perhaps the opposite?) purpose.

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8 July 1981; revised 2 September 1981

Intraventricular Calcitonin Inhibits Gastric Acid Secretion

Abstract. *Parenteral and intracerebroventricular administration of calcitonin in rats resulted in the suppression of gastric acid secretion. This suppression also occurred in rats with insulin-induced hypoglycemia and after the administration of thyrotropin-releasing hormone. Intracerebroventricularly administered calcitonin was 1000 times more effective than parenterally administered calcitonin in suppressing gastric acid secretion. Calcitonin also inhibited the development of stress-induced ulcers in rats.*

Calcitonin, a peptide hormone secreted from C cells within the mammalian thyroid, promotes absorption of calcium and phosphate into bone and acts in the conservation of skeletal calcium (*1*). A role for calcitonin as a neuromodulator in the central nervous system was suggested by the observations that radioactively labeled calcitonin that is administered parenterally binds specifically to sites in the hypothalamus (*2*) and that immunoreactive calcitonin is present in the hypothalamus and cerebrospinal fluid (*3*). Intracerebroventricular (ICV) administration of calcitonin potently suppresses feeding in rats (*4*), and parenterally administered calcitonin in animals and man inhibits gastric secretion (*5*). Physiological and pharmacological evidence indicates that the central and autonomic nervous systems play an important role in the modulation of gastric secretion (*6*), and several endogenous brain oligopeptides have been implicated as chemical messengers involved in the central nervous system modulation of

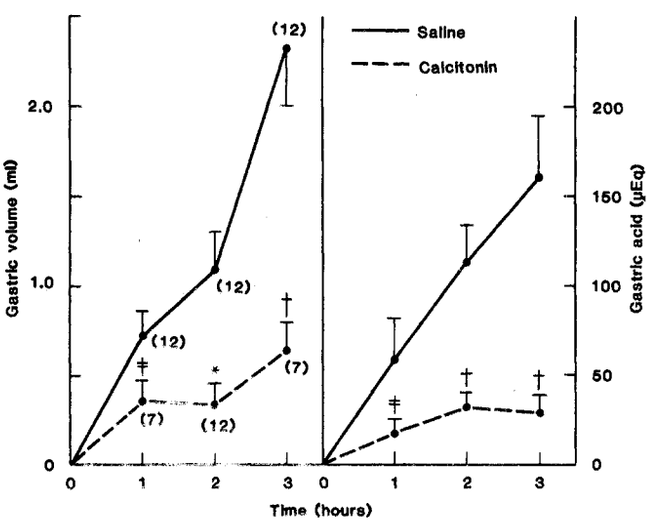

Fig. 1. Temporal effect of ICV administration of calcitonin (2 U, 416 ng) on gastric secretion. All results are expressed as means ± standard error (*$P < .001$, †$P < .01$, ‡$P < .05$). Numbers in parentheses refer to the number of animals at each time point. All animals were anesthetized with urethane (100 mg/kg) and the pylorus was ligated 1 hour later. Then intraventricular cannulas were inserted by using a stereotactic apparatus as described (*7*), and calcitonin (salmon, synthetic; Armour Pharmaceutical Co.) or saline was administered. The rats were killed 60, 120, or 180 minutes after the injection of calcitonin or saline. A two-tailed Student's *t*-test was used to determine statistical significance in all studies.

0036-8075/81/1106-0671$01.00/0

Table 1. Effect of ICV and parenteral (subcutaneous) administration of calcitonin on gastric secretion. All the animals were killed 2 hours after the injection. Experimental procedures were otherwise as described in Fig. 1.

Dose	*N*	Volume (ml/2 hours)	Acid (μEq/2 hours)
Saline (10 μl, ICV)	12	1.1 ± 0.2	111 ± 22
		ICV administration	
2 U	12	0.2 ± 0.1*	31 ± 8†
0.2 U	12	0.3 ± 0.1†	40 ± 14‡
0.02 U	12	0.4 ± 0.1†	49 ± 15§
0.002 U	8	0.4 ± 0.1†	42 ± 14§
0.0002 U	8	0.4 ± 0.1†	50 ± 12§
0.00002 U	8	1.1 ± 0.4	103 ± 27
		Parenteral administration	
10 μ/kg	7	0.3 ± 0.1†	26 ± 8‡
1 μ/kg	9	0.6 ± 0.2	55 ± 16
0.1 μ/kg	8	0.9 ± 0.2	84 ± 22

*$P < .001$. †$P < .01$. ‡$P < .025$. §$P < .05$.

gastric secretion (*7*). We report here that ICV administration of calcitonin potently inhibits gastric secretion. Central administration of calcitonin was approximately 1000 times more potent than parenteral administration, suggesting that calcitonin exerts its effects by a direct action on the central nervous system.

Male Sprague-Dawley rats (250 to 300 g) were given free access to Purina Lab Chow and tap water and housed under conditions of controlled temperature and illumination (0600 to 2000 hours). All experiments were performed according to the same time schedule in rats that had been deprived of food for 24 hours but given free access to water up to the beginning of the experiment. The animals were anesthetized with urethane (150 mg/100 g subcutaneously), and 1 hour later the pyloric portion of the stomach was ligated. Saline or test materials were injected intraventricularly into the lateral ventricle, intravenously via the jugular vein, or parenterally (subcutaneously). Two hours after injection (or at other specified time intervals) the esophageal-gastric junction was ligated and the whole stomach excised. Gastric volume and *p*H were measured and the samples analyzed for gastric acid by titration with 0.01*M* sodium hydroxide to a *p*H of 7.0.

As demonstrated in Fig. 1, two units of calcitonin (416 ng) administered ICV produced a marked suppression of gastric acid secretion by 1 hour after administration. This suppression was still evident 3 hours after administration of the calcitonin. Calcitonin administered by this route suppressed both gastric volume and gastric acid secretion in a dose as low as 0.0002 U (41 pg) (Table 1). In contrast, only the highest dose of parenterally administered calcitonin (10 U/kg) produced a statistically significant suppression of gastric acid secretion (Table 1). Thus, ICV administration of calcitonin was effective at a dose at least one-thousandth that of the parenteral dosage. We showed previously that there is a similar dose differential between parenteral and ICV administration in the suppression of food ingestion by calcitonin (*8*). These findings indicate that the major effect of calcitonin in reducing gastric secretion is on the central nervous system, which is in keeping with our previous observation that calcitonin reduces $^{45}Ca^{2+}$ uptake in hypothalamic explant cultures (*8*) at doses equivalent to the ICV doses that suppress gastric secretion.

We also examined the ability of calcitonin in rats to suppress gastric acid secretion induced by insulin and thyrotropin-releasing hormone (TRH), two substances which have been shown to produce gastric acid secretion by activation of the central nervous system (*7*) (Fig. 2). Both insulin and TRH produced the expected increase in gastric secretion compared to saline-treated controls. The ICV administration of calcitonin inhibited both insulin and TRH-induced gastric acid secretion to below basal levels, thus providing further evidence that calcitonin is a central inhibitor of gastric acid secretion.

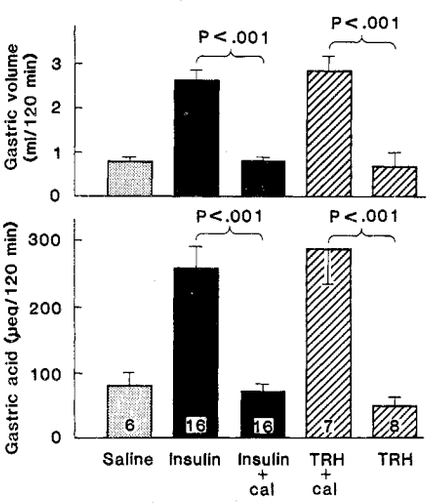

Fig. 2. Inhibitory effect of calcitonin on gastric output stimulated by insulin and TRH. Rats that had fasted for 24 hours received an ICV injection of calcitonin (2 U) or saline and then an injection of insulin (1 U, intravenously), TRH (5 μg, ICV), or saline (intravenously), after which the pylorus was ligated. Two hours later, the animals were decapitated. The bars represent means ± standard error; the number of animals in each group is shown at the base of each bar.

Ulceration induced by stress is an important clinical cause of upper gastrointestinal bleeding in man (*9*). However, the etiology of such ulceration is thought to be multifactorial and to include the interaction of gastric acidity, changes in gastric mucosal circulation, decreases in gastric epithelial cell turnover, and possibly a breakdown in the gastric mucosal barrier (*10*). The studies by Levine and Senay (*11*) have shown a strong correlation between low gastric *p*H and a high incidence of gastric lesions. On the basis of these concepts we decided to evaluate the effects of ICV calcitonin on the development of stress ulceration. We used 12 male Sprague-Dawley rats that had been food-deprived for 48 hours and then restrained in stress cages and exposed to cold (4°C) for 2 hours, after which time they were killed by decapitation. The animals had been prepared with cannulas inserted into the lateral ventricle 14 days before the experiment (*12*). Half of the animals received one ICV injection of saline and the other half, one ICV injection of calcitonin (2 U, 416 ng) immediately prior to being placed into the stress cages and the cold. When the animals were examined post-mortem, none of those that had received calcitonin had blood in the stomach and only one had two small gastric mucosal lesions less than 1 mm in size. All of the control animals had blood in the stomach and gastric mucosal lesions. The *J* score (*13*) for the control animals was 8.5 ± 2.0, whereas for the animals receiving calcitonin it was 0.3 ± 0.3 ($P < .001$). The lack of mucosal lesions in the animals that received calcitonin correlated with the increased *p*H (2.42 ± 0.2 compared to 1.25 ± 0.3 in controls, $P < .001$). From these observations it is apparent that ICV administration of calcitonin decreases the incidence of stress-induced ulcers in rats.

It appears reasonable to conclude that calcitonin suppresses gastric acid secretion by a direct action on the central nervous system. Because calcitonin enters the hypothalamus after parenteral

administration (*2*) and because calcitonin in the plasma increases after a meal (*14*), we suggest that calcitonin is partially responsible for inhibiting gastric acid secretion at the end of a meal.

The mechanism by which calcitonin alters central nervous system function is unknown. Myers *et al.* (*15*) have shown that feeding can be produced in the satiated rat by increasing the concentration of calcium in the brain. Recently, we have found that feeding induced by calcium chloride in the rat is inhibited by concomitant administration of calcitonin (*8*). In addition, using a hypothalamic explant culture system, we showed that calcitonin depressed $^{45}Ca^{2+}$ uptake at doses equivalent to the intraventricular doses that suppressed feeding and gastric acid secretion (*8*). It is thus tempting to speculate that calcitonin may produce its effects on the central nervous system by altering neuronal calcium fluxes.

The studies reported here together with those previously reported on the effects of calcitonin on food ingestion and on hypothalamic calcium fluxes strongly suggest a neuromodulatory role for calcitonin in the maintenance of hypothalamic activity. Thus, calcitonin should be added to the long list of peptides that play a role in integrating the hypothalamic functions responsible for the maintenance of the *milieu intérieur* (*16*). With the widening acceptance of the concept that calcitonin is a neuroactive hormone, it would not be surprising to find that it produced a number of other effects on the central nervous system.

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8 June 1981; revised 7 August 1981

Physical and Social Environment of Newborn Infants in Special Care Units

Abstract. *Infants in newborn intensive and convalescent care units are exposed to large amounts of sensory stimulation of various sorts. Although infants in these units do not lack visual, auditory, and tactile stimulation, they receive relatively infrequent coordinated sensory experiences. Furthermore, there is no diurnal rhythmicity in physical and social stimulation across days.*

Modern medical management has reduced neonatal mortality and morbidity. However, longitudinal investigations indicate that deficits in cognitive and sensory functioning persist as a major problem in the development of premature infants (*1*). Researchers have recently proposed that the intensive care unit, the environment in which many premature infants spend their early weeks, is not conducive to optimal development. Several investigators have hypothesized that the intensive care unit provides an environment that is inadequate in amount and pattern of stimulation (*2*). Contrary to this view, Cornell and Gottfried (*3*) contended that as a consequence of the personnel, equipment, and activity present in modern intensive care units, premature infants may be exposed to large amounts of sensory stimulation of various sorts. Lawson *et al.* (*4*) have suggested that premature infants in intensive care may suffer not from an inadequate amount of stimulation but from a disjunctive pattern of stimulation. Lucey (*5*) and Korones (*6*) have argued that intensive care may have become too intense and may be responsible for newly recognized iatrogenic complications. We now report an investigation of the quantity, quality, organization, and diurnal rhythmicity of physical and social stimulation in a special care unit for newborns in a major medical facility.

The study was conducted at Los Angeles County–University of Southern California Medical Center Women's Hospital. Observations were conducted in designated locations in the newborn intensive care (NICU) and convalescent care units (NCCU). Each unit houses between 18 and 25 infants. Three 1-minute observations in each unit were conducted at the same time every hour for 24 hours over three nonconsecutive days (two weekdays and one weekend day). For each observation, one researcher recorded physical and the other social data. The physical data included illumination levels (Gossen Luna Pro light meter), characteristic and peak sound levels (Bruel & Kjaer sound meter 2203), a frequency analysis of the sound spectra (Bruel & Kjaer octave filter set 1613), and occurrence of speech, nonspeech, and radio sounds (Table 1). These data were collected in operating incubators by means of the light and sound meters and by a tape recorder. The social data included the frequency of medical or nursing care, bottle-feeding, social touching, rocking, and talking when in contact with an infant; we also noted whether the infant was in a position to see the care giver (vision). Interobserver reliabilities for all physical and social variables exceeded 97 percent and 92 percent agreement, respectively.

The data base included a total of 405 recordings for each physical variable and 1551 observations of infants, of which 292 (18.8 percent) included social contact (*7*). There were no significant differences among the 3 days in the magnitude or frequency of events. Ambient cool-

0036-8075/81/1106-0673$01.00/0