initiating voluntary movements (*2*), its activation during a tonic contraction could be too short to be detected. This explanation is insufficient, however, since simple repetitive movements do not elicit activation either—in contrast to planned sequential movements and automatic but highly complex movements, which do (*9*).

The lack of SMA activation during silent counting makes it unlikely that internal speech may be responsible for the SMA activations measured in other test conditions. This result is of great importance since "internal programming" of a finger motor sequence in which the fingers are actually not moved activates the SMA and not the other motor or language areas (*6*). Considered together, these data imply a more specific involvement of the SMA in the programming of motor sequences rather than a mere relation of this area to internal language.

Our conclusion is that the SMA plays an important role in the initiation as well as in the regulation of some kinds of voluntary movements. The SMA may contribute to the establishment of new motor programs (*6*) and probably controls the execution of established subroutines according to external and internal inputs. Its anatomical connections and the available physiological data suggest that the SMA could be the place where external inputs and commands are matched with internal needs and drives to enable formulation of a strategy of voluntary movements. This concept, foreseen by Campbell (*14*) in 1905 from histological studies and by Sanides (*15*) in 1964 from embryological studies, is supported by recent studies (*16*) in which ablations of the SMA produced deficits in visually guided reaching behavior and by electrophysiological experiments (*17*) in which a role is suggested for the SMA in "readiness" to move, in the regulation of learned movements after sensory inputs, and as part of the neuronal circuit that elaborates some general features of movement performance. Thus, rather than restricting its role to tonic postural adjustments prior to movement, it seems compelling to consider the SMA as a supramotor area—a functional area of higher hierarchical order than the primary motor Rolandic areas.

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Calcitonin: Inhibitory Effect on Eating in Rats

Abstract. *Subcutaneous and intracerebral injections of calcitonin inhibited feeding in rats. The anorectic activity of calcitonin was destroyed by exposing the hormone to heat, trypsin, or hydrogen peroxide. Calcitonin did not produce a conditioned taste aversion to saccharin, and maximum inhibition of feeding occurred 4.5 to 8.3 hours after subcutaneous administration. It is concluded that calcitonin inhibits feeding by acting directly on the central nervous system.*

Cells within the mammalian thyroid, known as C cells, secrete the peptide hormone calcitonin (*1*). Since the discovery of calcitonin in 1961, the substance has been found to promote absorption of calcium and phosphate into bone as well as to act in the conservation of skeletal calcium (*2*). Because of these actions, it has been suggested that calcitonin has a physiological role in the prevention of hypercalcemia. In particular, calcitonin may prevent the postprandial hypercalcemia that otherwise would result from absorption of calcium from foods (*3*). Calcitonin may also promote mineralization of the skeleton by way of calcium absorbed from milk in preweanling animals (*4*). In support of these hypotheses, it has been demonstrated that plasma calcitonin concentrations increase after feeding in adult rats (*3*) and after suckling in infant rats (*4*). The fact that calcitonin is secreted postprandially suggested to us that calcitonin might participate in the regulation of subsequent feeding behavior. We studied this possibility by administering calcitonin to animals and found that calcitonin reduces feeding, apparently by a direct action on the central nervous system (CNS).

We previously reported (*5*) that calcitonin strongly inhibited 24-hour food intake of rats and rhesus monkeys when injected subcutaneously in relatively large doses (25 to 50 U/kg, or 5.3 to 10.6 μg/kg). In humans, a significant reduction in body weight was observed during the 24 to 36 hours following a single subcutaneous injection of 2 U/kg. In rats, the inhibition of feeding was dose-related (Fig. 1) and was accompanied by a pronounced diuresis.

To test the hypothesis that inhibition of feeding was due to a direct action on the CNS, we administered calcitonin to rats by intracerebroventricular injection (*6*) in dosages approximately 25 to 50-fold smaller than those that inhibited feeding when administered peripherally. Intake of food and water, excretion of feces and urine, and body weight were recorded during the 2 days before and after the injections.

The intracerebral injections produced large decreases in food intake for 24 hours (Fig. 1); the smaller dosage used (0.2 U or 43 ng) produced a 40 percent decrease in feeding ($P < .02$, Dunnett's multiple comparison). Fecal excretion and body weight decreased in parallel to the reductions in food intake (*7*). Drinking and urine excretion were unchanged, except that the largest dose (1 U) decreased drinking by 38 percent ($P < .01$).

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This contrasts with the effects of subcutaneous injections, which produced diuresis and an increase in drinking in the same dosages that reduced feeding.

To determine whether the anorectic activity of intracerebral calcitonin depends on the structural integrity of the calcitonin molecule, we measured food intake of rats after intraventricular injections of inactivated calcitonin (*8*). The amount of food (mean ± standard error) eaten during the 24 hours following injection was 30.8 ± 2.0 g for a group of six animals that received vehicle and 8.0 ± 1.3 g for six animals that received 213 ng of calcitonin ($P = 2.50 \times 10^{-6}$, two-tailed t-test). Animals that received calcitonin inactivated by incubation at 90°C for 18 hours, digested with trypsin (1 part in 500) at 25°C for 1 hour, or oxidized by incubation in 0.2*M* H_2O_2 at 37°C for 30 minutes ($N = 5$ per treatment) ate 27.8 ± 2.6, 22.0 ± 1.9, and 23.4 ± 2.4 g, respectively. Thus, treatments that have been shown to eliminate the hypocalcemic activity of the calcitonin molecule (*8*) essentially eliminate its CNS-mediated anorectic action.

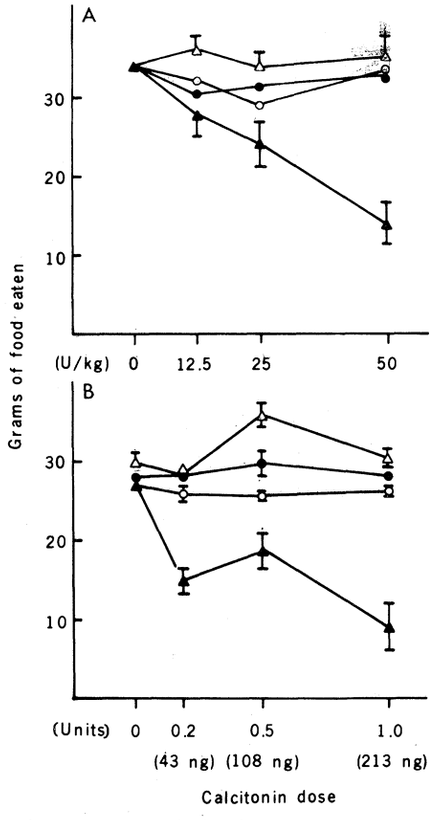

Fig. 1. Decreases in feeding produced by synthetic salmon calcitonin administered to rats by (A) subcutaneous or (B) intraventricular injection. Feeding was measured in terms of total 24-hour intake of pelleted Purina lab chow. Feeding during each of four consecutive days is indicated by a separate line: ●, 24 to 48 hours before; ○, 24 hours before; ▲, 24 hours after; and △, 48 hours after injection. Each point represents the mean of five to seven rats. Vertical bars indicate standard errors; some of these have been omitted for clarity. The effects of calcitonin were essentially restricted to the 24 hours after it was injected. During this period, the effect of subcutaneous calcitonin was statistically significant ($P = 8.21 \times 10^{-5}$, one-way analysis of variance), as was the effect of intraventricular calcitonin ($P = 1.62 \times 10^{-4}$).

In a second series of experiments, the time course of the anorectic effects of calcitonin was studied in a group of 12 rats that had been trained to ingest their entire food ration during a 30-minute period of each day. Once each week calcitonin (12.5 U/kg) or vehicle was administered by subcutaneous injection at various time intervals prior to feeding. Maximum inhibition of feeding occurred when the injections were given between 4.5 and 8.3 hours before feeding. When calcitonin was given 1, 3, or 22 hours before, feeding was not substantially decreased (Fig. 2). Thus, this dosage of calcitonin inhibits feeding only when it is administered several hours before food presentation. This suggests that calcitonin may act as a long-term influence on feeding, rather than as a short-term satiety signal.

We observed that almost all of the animals began to feed within 10 seconds of the food being introduced into the cages, regardless of whether they had received injections of calcitonin. This may suggest that they ate less because of a reduced eating rate or an earlier cessation of eating, rather than because they were sick or suffering from some debilitating effect of calcitonin (*9*). To determine whether or not calcitonin causes illness or aversive internal consequences, we used a "conditioned aversion" paradigm (*10*). This provides a measure of the aversive effects of drugs or other treatments: Ingestion of a preferred novel solution is reduced during the second exposure to that solution, whenever the first exposure to the solution has been followed by an aversive stimulus (such as lithium chloride) (*10*). In rats that were given access to water only during 15 minutes per day, we observed an 82 percent reduction in drinking ($P < .001$) of a 0.2 percent saccharin (novel) solution 24 hours after injections of lithium chloride (*11*). An attempt to use calcitonin as the aversive stimulus, however, was unsuccessful. Rats that received calcitonin (50 U/kg) subcutaneously after their first exposure to saccharin drank 6.8 ± 2.1 ml of saccharin 24 hours later; animals that received vehicle drank 7.0 ± 2.6 ml (*12*). Thus, calcitonin did not produce illness as measured by a conditioned aversion paradigm. Thus the calcitonin-induced reduction in appetite appears not to be the result of illness or aversive effects of the peptide, but to be a more specific property of the compound.

The findings reported here lead us to speculate that calcitonin has a specific physiologically relevant action in the CNS. We suggest this because: (i) inhibition of feeding by intracerebral calcitonin mimics the effects of peripheral injections, in a dosage range that is on the order of the proportion of the weight ratio of brain to total body mass (*13*); (ii) the dosages of intracerebral calcitonin that inhibit feeding are smaller than the minimum dosages of most other peptide hormones of extraneuronal origin [see (*14*)], such as adrenocorticotropic hormone, angiotensin II, and the enkephalins, that have previously been shown to induce behavioral alterations when administered into rat cerebral ventricles (*15*); (iii)

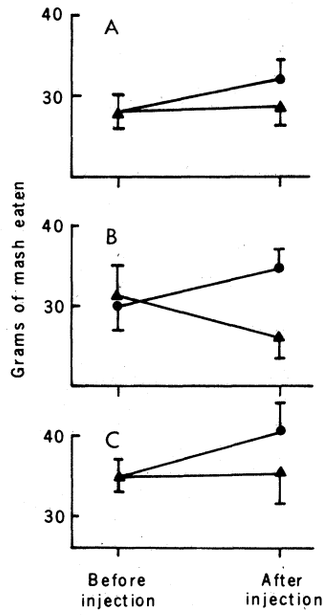

Fig. 2. Time course of the inhibition of feeding in rats deprived of food for 23½ hours by administration of synthetic salmon calcitonin (12.5 U/kg). Animals were allowed access to moist food (14 parts of ground Purina rat chow to 20 parts of water, by weight) for 30 minutes per day. The graph shows the amount of food eaten at (A) 1 hour, (B) 6 hours, or (C) 22 hours after injection and the amount of food eaten during the preceding day. Symbols: ●, rats that received vehicle and ▲, rats that received calcitonin. Each point represents the mean ± standard error of (C) six or (A and B) 12 rats. The difference in feeding was statistically significant for the 1-hour ($P < .05$, two-tailed t-test) and the 6-hour ($P < 0.1$) groups, but not for the 22-hour group ($P > .2$). In additional experiments (data not shown) feeding was significantly inhibited by injections 4.5 hours ($P < .01$) or 8.3 hours ($P < .001$) before feeding, but not by injections given 3 hours before feeding ($P > .2$).

inactivation of calcitonin by treatments expected to alter the characteristics of calcitonin as a peptide eliminated the ability of calcitonin to inhibit feeding; and (iv) such evidence as we have does not indicate that calcitonin inhibits feeding by producing illness or debilitation. It is therefore tempting to speculate that endogenous calcitonin is involved in the regulation of feeding and appetite, perhaps in certain specific situations such as during infancy, lactation, or calcium-specific hunger (*16*). However, further research will be necessary to determine whether the effects of calcitonin on feeding are merely pharmacological, or whether they mimic an effect of endogenously secreted calcitonin (*17*).

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6. Synthetic salmon calcitonin was administered by intraventricular injection [E. P. Noble, R. J. Wurtman, J. Axelrod, *Life Sci.* **6**, 281 (1967)] in normal saline in a volume of 10 μl. The synthetic salmon calcitonin used in all experiments was provided by Armour Pharmaceutical Company.
7. Decreases in fecal excretion ($P = 2.28 \times 10^{-3}$) were similar to the decreases in feeding. Body weight was also decreased on the day after injections ($P = 3.16 \times 10^{-5}$); the highest dosage (1 U) decreased body weight by 5.7 percent ($P < .01$) from a mean baseline weight of 366 g. Body weight recovered to a mean of 357 g on the second day after injections. This temporary body weight loss was apparently related to the decrease in feeding and the associated decrease in fluid intake.
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9. We were unable to produce observable deficits in motor coordination in rats and in mice with subcutaneous injections of calcitonin in amounts up to 200 U/kg. W. J. Freed, M. J. Perlow, J. S. Carman, R. J. Wyatt, paper presented at the 8th annual meeting of the Society for Neuroscience, St. Louis, 1978.
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11. Rats received 300 mOsm LiCl or NaCl (20 ml/kg) immediately after their first access to saccharin. After 24 hours the animals that had received lithium drank 2.0 ± 1.2 ml of saccharin solution, whereas the animals that received sodium drank 11.0 ± 1.4 ml.
12. The two groups drank approximately equal amounts on the first exposure to saccharin; 8.3 ± 1.7 ml for the animals that received calcitonin and 8.3 ± 1.2 ml for the animals that received vehicle.
13. As determined by linear regression, the ED_{50} (50 percent effective dose) for inhibition of feeding was 1.86 U/kg administered intraventricularly and 46.3 U/kg administered subcutaneously.
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17. Myers and his colleagues [R. D. Myers, S. A. Bender, M. K. Krstic, P. D. Brophy, *Science* **176**, 1124 (1972); R. D. Myers, C. L. Melchior, C. V, Gisolfi, *Brain Res. Bull.* **1**, 22, (1976)] have reported that perfusion of calcium into brain extracellular fluid provokes feeding in animals and have suggested that feeding is related to the ratio of calcium to sodium in brain extracellular fluid. It has also been suggested that the primary action of calcitonin (in nonneuronal tissues) is to redistribute calcium from extracellular to intracellular fluid [H. Rasmussen and M. Pechet, *International Encyclopedia of Pharmacology and Therapeutics* (Pergamon, New York, 1970), section 51, vol. 1, p. 237]. If calcitonin similarly influences calcium distribution in the brain, it might decrease feeding through decreasing the ratio of extracellular calcium to sodium in the brain.
18. We thank L. A. Bing for technical assistance and J. P. Aldred of the Armour Pharmaceutical Company for comments and suggestions.

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Humans Deprived of Normal Binocular Vision Have Binocular Interactions Tuned to Size and Orientation

Abstract. *A suprathreshold grating presented to one eye elevated the threshold for the discrimination of gratings similar in size and orientation presented to the fellow eye. The magnitude and stimulus specificity of these binocular interactions in human observers with normal binocular vision were similar to those in observers deprived of normal binocular visual experience; however, the latter showed a failure of binocular summation at threshold or subthreshold contrast levels. Whereas strabismus or amblyopia disrupted the normal excitatory interactions between the two eyes, cortical inhibitory binocular connections seem not to have been disrupted.*

Most neurons in the visual cortex of cats and monkeys receive inputs from both eyes. For a given binocular cell, the stimulus requirements (such as size and orientation) are usually similar for the two eyes (*1*). These binocular connections are functionally present at birth, but are refined by concordant binocular experience during a critical period of development (*2*). In contrast, in animals deprived of normal binocular vision through experimentally induced strabismus or monocular form deprivation (resulting from lid closure or anisometropia), most neurons encountered have only a monocular input (*3*). Recent evidence suggests that this reduction in cortical binocularity may be in part the result of synaptic inhibition (*4*).

Several lines of psychophysical evidence have also implied a reduced number of binocular neurons in humans deprived of normal visual experience due to a naturally occurring strabismus or anisometropia. For example, such individuals are frequently stereoblind, display reduced interocular transfer of certain visual aftereffects, and show a failure of binocular summation on visual threshold tasks (*5*). In addition, they retain information concerning the eye of origin under conditions in which normal observers are unable to make reliable distinctions (*6*). On the other hand, it has been suggested from clinical observations that many strabismics in fact show inhibitory binocular interactions; that is, they suppress the input from one eye, and the suppression is most marked for similar stimuli (*7*). We have investigated the nature and extent of binocular interactions in humans deprived of normal visual experience by strabismus, amblyopia, or both. The results show that they have binocular interactions narrowly tuned to size and orientation and similar in magnitude and bandwidth to those found in normal observers.

Observers viewed two matched cathode-ray tube displays in a mirror stereoscope. Each eye was presented with an unstructured 8° circular field with a mean luminance of 10 cd/m^2 (unchanged when test patterns were presented). By depressing a button, the observer initiated a pair of 500-msec trials separated by 1 second. Each trial was delimited by a tone. In both trials, one eye was presented with a background of either a blank field or a grating. A test grating was also presented to the other eye on one of the two trials. Both the background and test gratings could be independently varied in spatial frequency,

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