percent) corresponds to the distribution of right- and left-handedness in adults. The neonate's head-orientation preference, which is maintained for at least 2 months after birth, reliably predicts the infant's preferred hand when reaching for objects. Therefore, a majority of infants prefer to use their right hands for reaching.

The mechanism linking infant head-orientation preference to hand preference in reaching was not identified in this study. However, infants who keep their heads turned to the right see their right hands more often than their left (*9*). With more opportunity to observe their right hands, infants may develop better eye-hand coordination with that hand, thereby giving it an advantage over the left in visually guided reaching. Thus, head-orientation preference could be associated with hand preference because of differences in visuomotor experience of the hands. Alternatively, head orientation and handedness could be independently determined by the same underlying factor. This latter interpretation would require two underlying factors, one for the right and one for the left preferences. This traditional two-factor model, unlike Annett's single-factor model, fails to account adequately for the distribution of handedness among the offspring of two left-handed parents.

An association between head-orientation preference and handedness is compatible with Annett's genetic model if we assume that head orientation, rather than handedness, is directly affected by the right-biasing factor. As such, the absence of the factor responsible for the right bias in head-orientation preference should result in a random binomial distribution of both head-orientation preferences and, subsequently, handedness. Within individuals, however, handedness and head-orientation preference should still be associated as they were in this study.

Although the results of this short-term longitudinal study do not disclose the relation between infant hand preferences and adult handedness, head-orientation preferences of supine infants did predict the early development of handedness and probably contribute to the development of the right bias in human handedness.

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Cholecystokinin Antibody Injected in Cerebral Ventricles Stimulates Feeding in Sheep

Abstract. *The role of brain cholecystokinin peptides in satiety was further assessed by using antibody to cholecystokinin to reduce cholecystokinin activity in the cerebrospinal fluid of sheep. Food intakes were increased approximately 100 percent during the 2-hour continuous injection of antibody into the cerebrospinal fluid. This supports the hypothesis that, during feeding, cholecystokinin is released into the cerobrospinal fluid, which transports it to the receptors that elicit satiety.*

Cholecystokinin (CCK) peptides are present in both the brain and the gastrointestinal tract (*1, 2*). Although many of the functions of intestinal CCK are well documented, those for brain CCK peptides are only now being investigated. The primary form of CCK in the brain, CCK-octapeptide (CCK-OP), is present in discrete areas in the cortex, thalamus, hypothalamus, mesencephalon, and brainstem (*3*), and specific CCK receptors appear to be distributed among many of the same areas (*4*). Certain properties of brain CCK-OP suggest that this peptide may have neurotransmitter or neurohormonal functions; it is concentrated in the synaptosome-rich fractions, and its release is calcium-dependent (*5*).

There is evidence that brain CCK-OP is important in the control of food intake. When administered as a continuous lateral cerebral ventricular (LV) injection, CCK-OP is a potent suppressor of feeding in sheep; femtomole amounts of this peptide significantly decrease food intake in sheep (*6*). The effect of CCK-OP is specific for feeding behavior, since neither drinking nor body temperature is affected (*6*). In addition, only peptides meeting the minimum structural requirements for CCK activity peripherally decrease feeding behavior when administered centrally, thus supporting the concept that specific CCK receptors in the brain mediate the effect on feeding behavior (*7*).

In rats, experimental results are conflicting. Stern *et al.* (*8*) and Maddison (*9*) showed that CCK peptides injected centrally decreased food intake in rats, whereas we (*6*) and others (*10, 11*) have found no effect. McCaleb and Myers (*12*) showed that intrahypothalamic injections of CCK suppressed feeding behavior that was elicited by norepinephrine subsequently injected in the same sites. This suggests that CCK acts directly on hypothalamic noradrenergic systems to mediate its effect on feeding. Although Schneider *et al.* (*13*) found no difference, Straus and Yalow (*14*) reported a lower concentration of CCK-OP in brains of genetically obese mice *(ob/ob)* compared to their lean littermates *(OB/−)* and have also shown that starved mice have reduced brain CCK-OP concentrations in comparison with fed mice. Thus, the role of CCK in the brain of rodents in the control of feeding is controversial.

On the basis of the results of our studies in sheep, we have proposed that CCK-OP is released during meals and acts as a signal of satiety (*6*). The demonstration that behavior indicating satiety follows administration of exogenous peptide is not sufficient to prove that endogenous CCK-OP participates in feeding behavior, however. Thus, we have carried out experiments to deter-

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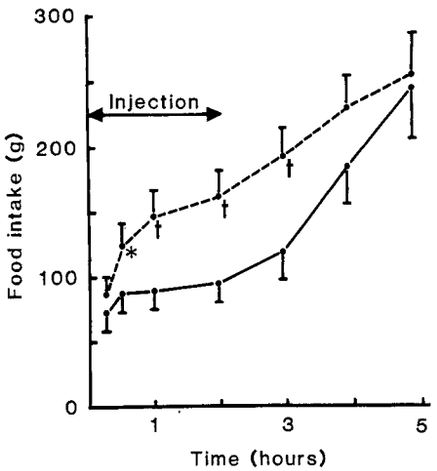

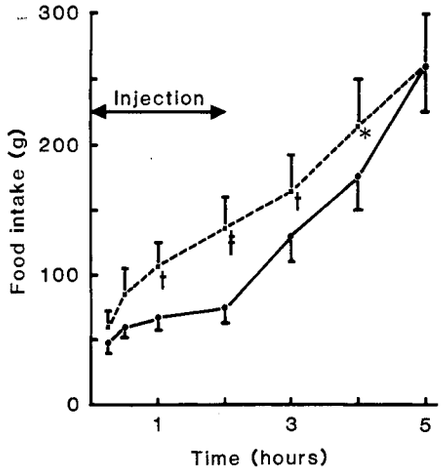

Fig. 1 (left). Food intake of satiated sheep during continuous lateral ventricular injection of CCK-AB-1 at a CCK-OP binding capacity of 24 pg per 0.03 ml (---) and of control rabbit serum in synthetic CSF (—). The injections were delivered at a rate of 0.03 ml/min for 2 hours; the values are means ± standard error (S.E.) for nine sheep in each group. Fig. 2 (right). Food intake of satiated sheep during continuous lateral ventricular injection of CCK-AB-2 at a CCK-OP binding capacity of 24 pg per 0.03 ml (---) and of control rabbit serum in synthetic CSF (—). The injections were delivered at a rate of 0.03 ml/min for 2 hours; the values are means ± S.E. for 16 sheep in each group. Symbols: *, $P < .10$; †, $P < .05$; and ‡, $P < .01$.

mine the role of endogenous brain CCK-OP in satiety; continuous LV injections of antibody to CCK-OP (CCK-AB) in amounts that would bind only a few picograms of CCK-OP per minute caused significant increases in food intake in satiated sheep. These results not only provide strong support for a physiological role for brain CCK-OP in satiety, but also suggest that transport of the peptide from sites of release to sites of action occurs by way of the cerebrospinal fluid (CSF).

Castrated male sheep (wethers, 30 to 40 kg; $N = 16$) were prepared surgically with permanent LV cannulas (*15*) and were given at least 3 weeks to recover. They were housed in individual stalls in a room with constant light and temperature (21°C) and were given free access to a complete pelleted ration (*6*). Water was also freely available. On treatment days, the sheep were given additional food, which stimulated the sheep to eat a meal; this meal served to synchronize feeding. The food was then removed for 2 hours, and the sheep were prepared for injection (*6, 16*). Before the injections were begun the sheep were again permitted to eat for 15 minutes, which is the normal length of a meal for sheep fed this ration (*17*). Solutions were administered by means of syringe pumps at a rate of 0.03 ml/min for 2 hours.

Treatments, consisting of control and CCK-AB solutions, were randomly assigned in a crossover design. The antibodies were raised in rabbits to the synthetic desulfated CCK-OP and were shown to react equally, on a molar basis, with CCK-OP, human gastrin I, and porcine CCK-33. Somatostatin, arginine vasopressin, methionine enkephalin, adrenocorticotropin, gonadotropin-releasing hormone, and thyrotropin-releasing hormone all failed to inhibit the binding of ^{125}I-labeled CCK-OP to the antibody (*13*). The antiserum was administered in a synthetic CSF solution (*18*), which had been filtered through a Millipore filter to ensure sterility. The control solutions consisted of synthetic CSF with rabbit serum from a nonimmunized rabbit added in a volume equal to that of the CCK-OP antiserum. (Treatments with synthetic CSF with and without serum added showed no differences in food intakes; therefore, serum itself had no effect on feeding.) Three doses of CCK-AB-1 were tested; the approximate binding capacities in vitro were 24, 6, and 1.5 pg of CCK-OP for the quantity of antiserum injected each minute. Antiserum from another immunized rabbit was also tested (CCK-AB-2) at an injection rate providing an approximate in vitro binding capacity of CCK-OP of 24 pg/min; this was done to determine whether any effect of CCK-AB-1 on feeding was due to the serum from that particular rabbit. Paired *t*-tests were used to evaluate the significance of the treatment effect.

Food intakes were significantly increased during injection of both CCK-AB-1 and CCK-AB-2 at the CCK-OP binding capacity of 24 pg/min (Figs. 1 and 2). The pattern of the increase in food intake suggests that satiety was inhibited by injection of the antibodies, since a typical postmeal interval occurred during control injections (hours 0 to 2), whereas during CCK-AB injections, the sheep continued to eat at a rapid rate for at least 1 hour after the injections were started. Food intakes were significantly increased for 1 hour after the end of injection, and there was a trend for intake to remain increased for up to 2 hours after the end of injection. Since CCK-AB-1 and CCK-AB-2 both stimulated feeding, the effect was not specific for the serum from a particular rabbit.

Food intakes were also increased during injection of CCK-AB-1 at a CCK-OP binding capacity of 6 pg/min. Food intakes were increased more than 150 percent throughout the injection period ($P < .05$), and there was a trend ($P < .10$) for an increased food intake for up to 1 hour after the end of injection. Feeding was not affected by CCK-AB-1 at the CCK-OP binding capacity of 1.5 pg/min.

In experiments with rats, bolus injections of CCK-AB-1 into the lateral ventricles had no effect on food intake (2 hours after injection: saline, 5.02 ± 1.14 g; CCK-AB-1, 4.64 ± 1.26 g). It may be important to note that bolus injections of CCK-OP in the lateral ventricles did not depress food intake of rats (*10*) or sheep (*16*), but in pigs 0.48- to 1.9-nmole bolus injections into the cerebral ventricles reduced feeding in a dose-related manner (*19*).

These results suggest that brain CCK peptides, possibly CCK-OP, have a physiological role in satiety in sheep. Since the size of the antibody molecules makes it unlikely that they can penetrate the ependyma, in order for LV injections of CCK-AB to affect feeding, CCK peptides would have to enter the CSF before interacting with CCK receptors. Evidence has been accumulating for an active, rather than passive, role for CSF in the movement of certain peptides. For example, removal of vasopressin from the CSF by LV injection of antiserum to vasopressin inhibited memory expression in rats (*20, 21*). In these studies, as in ours, a CSF route of transport for the peptide would be necessary for the antibody to be effective.

We have measured CCK-OP-like immunoreactivity in CSF from satiated sheep in concentrations of approximately 12 pg/ml (*22*). If the CSF production rate in sheep is similar to that in goats (0.2 ml/min) (*18*), an estimate of the CCK-OP secretion rate would be 2.4 pg/min. Thus the highest dose of CCK-AB injected would have been enough to bind ten times the estimated amount of CCK-OP secreted per minute and the lowest

effective dose, enough to bind 2.5 times the amount of CCK-OP secreted per minute. Although the antibodies used in these experiments bind gastrin (*13*), it is unlikely that binding of gastrin in the CSF [which is reportedly present only in the neuro- and adenohypophysis (*1*)] contributed to the increase in food intake, since we had previously found that only very high doses of pentagastrin, when injected into the LV, decreased food intake in sheep, and these doses caused abnormal behaviors (*6*). In addition, desulfated CCK-OP had no effect on feeding at doses equivalent to those that decreased feeding at least 80 percent when sulfated CCK-OP was used. Caerulein, CCK-OP, and CCK-33 were all effective in decreasing feeding (*9*). Therefore there appears to be a strict structural requirement for CCK-like peptides to elicit satiety, making it unlikely that gastrin in the CSF would influence feeding behavior.

We propose that the food intake increase caused by CCK-AB was a direct result of the binding of CCK peptides in the CSF by the antibody molecules, preventing them from binding to receptors involved in satiety. This finding supports our hypothesis that, during feeding, CCK-OP or another CCK peptide in the brain is released into the CSF and then travels to the site of action for eliciting satiety. The inability to demonstrate a similar response in rats suggests that CCK-OP may function as a neuromodulator of satiety in some species but not in others.

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Stress-Induced Analgesia in Humans: Endogenous Opioids and Naloxone-Reversible Depression of Pain Reflexes

Abstract. *The cumulative effects of a repetitive stress induced by anticipation of pain (noxious foot shock) were studied on the threshold of a nociceptive flexion reflex of the lower limb. The threshold of the nociceptive reflex progressively increased with the repetition of the stress. This effect was reversed by naloxone, which even produced hyperalgesia, since a rapid and significant decrease in this threshold, below the initial values, was noted. The data provide evidence for involvement of endogenous opioids in the phenomenon of stress-induced analgesia in normal man.*

Some specific psychological conditions, stress and anxiety, can modify the perception of pain and spinal excitability (*1*). These modifications have been partly explained in terms of activation of central nervous structures such as reticular formation or limbic system (*2*). The progress made in understanding the anatomy and physiology of pain modulation led some investigators to examine the effects of stress in relation to endogenous opioids in animals. Rats subjected to intermittent and inescapable stress, noxious foot shock, showed a significant increase in the opiate-like activity of the whole brain as well as in an analgesia, as judged by the increase in the latency of tail flicking (*3*). These effects were partially blocked by strong doses of naloxone.

Our study, performed in humans, gives further evidence for involvement of opioid mechanisms in stress-induced analgesia, since we observed a naloxone-reversible depression of nociceptive reflexes with intermittent and repetitive stress (anticipation of inescapable and very noxious foot shock). For this study, six healthy adults (four men and two women, 22 to 35 years of age) were volunteers.

The neurophysiological procedure for eliciting and recording nociceptive reflexes from the lower limb has been described (*4*). Briefly, the sural nerve was stimulated with surface electrodes placed on the scratched and degreased skin (2 cm apart) at its retromalleolar path. The stimulus consisted of a train of ten shocks of 1 msec duration each (300 Hz of internal frequency) delivered by a constant-current stimulator at a rate of 0.2 cycle per second. Nociceptive flexion reflexes were recorded from a flexor muscle of the lower limb (biceps femoris muscle) by a pair of surface electrodes placed on the skin above the muscle. The reflex threshold was then defined as the stimulus intensity eliciting 70 to 80 percent of the responses in the biceps femoris muscle. This method was chosen because the threshold of the nociceptive reflex from the biceps femoris muscle is homogeneously stable at 10 ± 1 mA in normal trained volunteers and is well correlated with a pricking pain sensation elicited by a noxious sural stimulation (*4*). Thus, this method could allow the study of suprasegmental influences on nociceptive reflex activity as an objective index of pain behavior in humans (*5*).

The stress was induced by a 2-minute warning period announcing the rapid occurrence of a very noxious and inescapable electrical stimulation (70 mA) applied to the sural nerve. Subjects then received either the expected stimulus or a tactile one randomly distributed. This stressful anticipation of incertitude of pain was preceded by a 2-minute resting period during which the subjects were ordered to relax. These rest-stress periods were repeated 19 to 20 times during sessions of 80 to 90 minutes. All subjects were tested at least three times at weekly

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