part, to a relatively limited capacity to increase cellular energy metabolism at elevated temperatures (*13*). This deficit would be markedly increased during seizures and could contribute to the brain damage associated with febrile-status epilepticus in very young children (*3*, *4*). Functional neurological deficits, including decreased maze-solving ability and increased sensitivity to other epileptogenic stimuli, occur as sequelae to hyperthermic seizures in the rat pup (*6*). Further studies of the pathogenesis of hyperthermic seizures and their sequelae in the immature rat and in higher mammals may help to answer important clinical questions concerning febrile convulsions in young children.

DAVID HOLTZMAN
KATHRYN OBANA
JAMES OLSON
Departments of Neurology and *Pediatrics, Stanford University School of Medicine, Stanford, California 94305*

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8. Brain and rectal temperatures were measured in at least four animals at each age during continuous warming in the Lucite chamber. In 2-day-old pups, brain temperatures were 0.25° to 0.50°C higher than rectal temperatures during warming from 33° to 42°C. In 5- and 7-day-old animals, brain temperatures were consistently 0.5° to 1.0°C lower than rectal temperatures at rectal temperatures above 38°C. In 10-day-old pups, brain and rectal temperatures were the same at rectal temperatures above 40°C. These small dissociations were due to the warming conditions, since these temperatures were the same in 6-day-old pups warmed to 41° and 45°C in a constant-temperature chamber.
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Abdominal Vagotomy Blocks the Satiety Effect of Cholecystokinin in the Rat

Abstract. *The site where peripherally administered cholecystokinin-8 elicits satiety was investigated by injecting rats with cholecystokinin-8 (1 to 8 micrograms per kilogram of body weight, intraperitoneally) after they had received bilateral lesions of the ventromedial hypothalamus or after they had undergone bilateral abdominal vagotomy or selective vagotomies. Abdominal vagotomy or gastric vagotomy abolished or reduced the satiety effect of cholecystokinin, but lesions of the ventromedial hypothalamus did not. These results demonstrate that peripherally administered cholecystokinin acts in the abdomen through gastric vagal fibers and not directly on the brain to produce satiety in the rat.*

Cholecystokinin (CCK), a peptide present in the central nervous system and gut, inhibits food intake in animals and humans after it is centrally (*1–3*) or peripherally administered (*4*). The site of action of this effect is controversial. After central administration, CCK-8 presumably acts on brain CCK receptors (*5*), although Nemeroff *et al.* (*6*) concluded that centrally administered CCK-8 inhibited tail pinch–induced feeding by acting at a peripheral site. It has been suggested that CCK-8 also acts in the brain (*2*), particularly in the ventromedial hypothalamic area, after it is administered peripherally (*3*). However, Kulkosky *et al.* (*7*) observed a normal satiety effect of peripherally administered CCK-8 in rats with bilateral lesions of the ventromedial hypothalamus (VMH). We have further investigated the site of action of peripherally administered CCK-8 (*8–10*) and report here that peripherally administered CCK-8 has a peripheral site of action in an abdominal organ innervated by the gastric vagal nerves.

Male Sprague-Dawley rats (300 to 500 g) were subjected to bilateral abdominal vagotomy and female Sprague-Dawley rats (225 to 275 g) received electrolytic lesions of the VMH (*11*). Testing began 1 month after surgery, when all vagotomized rats had stable intakes of food and water and looked healthy. Ten of 12 rats with VMH lesions were hyperphagic in the first 2 weeks after surgery (daily sweet milk intakes > 2 standard deviations larger than control). Eight of these hyperphagic rats were selected randomly and placed on restricted food intake to maintain body weight close to that of rats that received sham operations.

For each test, the vagotomized rats were offered a test diet (Gibco, EC116)

Table 1. Effect of abdominal vagotomy or ventromedial hypothalamic (VMH) lesions on CCK-induced satiety. The data (means ± standard error) show the percentages of inhibition of food intake. The percentage of inhibition of food intake = 100 × 1 − 30-minute intake after CCK-8/30-minute intake after saline.

Group	*N*	Dose of CCK-8 (μg/kg)			
		1	2	4	8
Controls	16*	20 ± 9	31 ± 8	60 ± 6	54 ± 9
VMH lesion	8	22 ± 12	20 ± 14	62 ± 7	60 ± 8
Vagotomy†	8	−14 ± 18	2 ± 15	16 ± 15	7 ± 16

*N = eight controls for hypothalamic lesions and eight controls for vagotomy; since there was no difference in the intakes of the two groups, their data were pooled. †Group mean differs significantly from controls ($P < .01$) and VMH lesion ($P < .05$) by Tukey test after analysis of variance (*14*). Analysis of variance was significant for the group effect, $F(2, 29) = 7.51$, $P < .01$, and for dose, $F(3, 42) = 8.45$, $P < .01$, but not for the interaction ($P > .10$). Negative inhibition indicates rats ate more after this dose of CCK-8.

Table 2. Effect of selective vagotomies on CCK-induced satiety. The data (means ± standard error) show the percentages of inhibition of food intake.

Group	*N*	Dose of CCK-8 (μg/kg)			
		1	2	4	8
Controls	11	22 ± 5	43 ± 6	44 ± 4	67 ± 4
Total*	7	22 ± 6	−13 ± 16	−8 ± 17	17 ± 11
Gastric*	11	4 ± 10	11 ± 11	18 ± 14	10 ± 8
Coeliac	8	14 ± 4	31 ± 6	41 ± 12	56 ± 7
Hepatic	5	16 ± 15	41 ± 10	31 ± 8	56 ± 7
Coeliac plus hepatic	7	22 ± 10	27 ± 15	61 ± 10	47 ± 7

*Total and gastric vagotomies differ significantly from controls (Tukey test, $P < .01$) after analysis of variance. Analysis of variance was significant for the group effect, $F(5, 43) = 13.25$, $P < .01$, and for dose, $F(3, 129) = 7.00$, $P < .01$, but not for the interaction ($P > .10$).

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and the rats with VMH lesions were offered a sweet milk diet after 17 hours of food deprivation. Intakes were measured at 15-minute intervals for 1 hour. Fifteen minutes before food was presented the rats were injected intraperitoneally with a dose of synthetic CCK-8 or with an isovolumetric injection of isotonic saline. The results were clear-cut: bilateral vagotomy reduced or abolished the satiety effect of CCK-8, but VMH lesions did not (Table 1). The hypothalamic lesions extended beyond the VMH area in all cases and sometimes included the paraventricular nucleus, medial preoptic, and suprachiasmatic areas. Thus, none of the structures in the ventromedial portion of the anterior and tuberal hypothalamus are necessary for the satiety effect of CCK-8. This supports and extends the earlier report of Kulkosky *et al.* (*7*).

This experiment demonstrated that peripherally administered CCK-8 acted at a vagally innervated site below the diaphragm and not in the brain. Lorenz and Goldman (*12*) also observed loss of the satiety effect of CCK-8 after abdominal vagotomy, but Anika *et al.* (*13*) did not. It is possible that the different results reflect differences in the vagal denervation of a specific visceral structure that CCK-8 acts on to initiate the signal for satiety.

In a second experiment we investigated which vagal branches were necessary for the satiety effect of CCK-8 by comparing the effect of selective transection (*11*) of the hepatic, coeliac, hepatic and coeliac, or gastric vagal branches with the effect of bilateral abdominal vagotomy on the satiety action of CCK-8. Rats were maintained and tested under the conditions of the first experiment and testing began about 1 month after surgery. Gastric vagotomy was the only selective transection that blocked the satiety effect of CCK-8 just as effectively as bilateral abdominal vagotomy (Table 2). Our finding that CCK-8 produced the normal satiety effect in hepatic and coeliac transected rats that had only the gastric vagal branches intact indicate that the gastric vagal branches are necessary and sufficient for the satiety action of CCK-8. This suggests that the stomach is the site of CCK-8 action, but since the gastric vagal branches also innervate the first part of the duodenum, the liver, and the head of the pancreas, these sites must also be considered.

It is not clear if the critical lesion involves the gastric efferent fibers, the gastric afferent fibers, or both. Since the efferent and afferent fibers cannot be transected selectively in the abdomen, we used atropine methyl nitrate to produce peripheral anticholinergic blockade that may mimic the loss of cholinergic vagal efferent fibers. Test conditions were the same as in the first two experiments except that rats that received no surgery were given an intraperitoneal injection of atropine methyl nitrate (5 mg/kg) or saline 15 minutes before they received CCK-8. Atropine methyl nitrate did not change the satiety effect of CCK-8 [percentages of inhibition of intake for 30 minutes were as follows: after CCK-8 (4 μg/kg) preceded by saline, 26 ± 2.8; after CCK-8 (4 μg/kg) preceded by atropine, 28 ± 3.4; after CCK (8 μg/kg) preceded by saline, 44 ± 6.5; and after CCK (8 μg/kg) preceded by atropine, 44 ± 5.5]. The lack of effect of atropine methyl nitrate suggests, but does not prove, that transection of vagal afferent fibers is the critical lesion.

From these experiments we hypothesize that intraperitoneally administered CCK-8 produces satiety by activating vagal afferent nerves through direct effect on afferent terminals or receptors, or through an effect on smooth muscle that stimulates gastric vagal afferent receptors. By inference, this vagal mechanism would also be activated by circulating, endogenous CCK-8 released by food stimuli in the small intestine.

G. P. SMITH*
C. JEROME
B. J. CUSHIN†
R. ETERNO
K. J. SIMANSKY
Cornell University Medical College and *New York Hospital–Cornell Medical Center, Westchester Division, White Plains 10605*

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The gastric branches or coeliac branch were transected in a similar manner. The highest point of section of the gastric branches was along the lower esophagus below the hepatic branch on the right and the coeliac branch on the left. The coeliac branch was sectioned as it entered the coeliac bundle. The bundle was then dissected and a suture placed around the most prominent nerve fibers at a point about 1 to 2 cm distal to where the coeliac branch entered the bundle. The fibers between the sutures were removed and the artery and vein were stripped.
All the vagotomies were verified anatomically by G.P.S. after testing was completed. Each rat was killed with a toxic dose of Chloropent. The vagal trunks were identified in the thorax and traced into the abdomen. The sutures were located and the gap between the sutures was searched (×6 to ×40 magnification). If a single ambiguous fiber crossed the gap between sutures we assumed that vagotomy was incomplete and discarded the results from the rat. A search was also made for unusual branches, such as a coeliac branch from the right trunk.
Ventromedial hypothalamic lesions were made by passing 1-mA anodal current for 15 seconds through a 00 insect pin that was insulated to within 0.5 mm of its tip. With the skull horizontal, these stereotaxic coordinates were used: bregma − 2.8, lateral midsagittal suture RL 0.6, and 9.2 down from the skull.
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* Send requests for reprints to E. W. Bourne Behavioral Research Laboratory, New York Hospital, 21 Bloomingdale Road, White Plains 10605.
† Present address: Department of Plastic Surgery, Montefiore Hospital and Medical Center, Bronx, N.Y. 10467.

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