

Peptides that Regulate Food Intake

Norepinephrine is not required for reduction of feeding induced by cholecystokinin

C. Matson Cannon and R. D. Palmiter

Department of Biochemistry, Howard Hughes Medical Institute,
University of Washington, Seattle, Washington 98195-7370

Submitted 8 November 2002; accepted in final form 27 February 2003

Cannon, C. Matson, and R. D. Palmiter. Norepinephrine is not required for reduction of feeding induced by cholecystokinin. *Am J Physiol Regul Integr Comp Physiol* 284: R1384–R1388, 2003; 10.1152/ajpregu.00689.2002.—CCK octapeptide (CCK-8) is released by the gut in response to a meal and acts via CCK_A receptors on vagal afferents to induce satiety. However, the central neural pathways by which peripheral CCK-8 affects feeding are poorly understood. In the present study, we tested the hypothesis that norepinephrine (NE) is necessary for satiety induced by peripheral CCK-8 by using mice lacking dopamine β-hydroxylase (*Dbh*^{-/-}), the enzyme responsible for synthesizing NE and epinephrine from dopamine. We found that *Dbh*^{-/-} mice are as responsive to the satiating effects of CCK-8 as their normal littermates.

knockout mice; cholecystokinin-8; norepinephrine; dopamine β-hydroxylase

CHOLECYSTOKININ OCTAPEPTIDE (CCK-8), often referred to as a “satiety signal,” is important in the control of meal size (45). Exogenous CCK-8 potently reduces meal size and duration in many animals, including mice, rats (12), and humans (19). However, it has been reported that CCK-8 alone does not cause body weight loss, because, despite persistently reduced meal size, meal number is increased and body weight is defended (54). In contrast, when CCK-8 is given in combination with leptin, body weight reduction is greater than that observed with leptin alone (27–29). Similarly, hypophagia caused by CCK is enhanced by concurrent administration of leptin or insulin (1, 11, 43) and reduced by extended fasting (33). Thus the effects of CCK-8 depend on the context of energy balance.

CCK-8 is released by the gut in response to a meal and acts via CCK_A receptors on the vagus nerve (20, 47). Vagal afferents are glutamatergic (40, 49), and all CCK_A receptor-expressing vagal neurons also express cocaine- and amphetamine-regulated transcript (8).

From this point, the transduction of the “satiety signal” is not well understood. Expression of the immediate early gene *c-fos* has been used as an index of enhanced neuronal activity after CCK-8. Large doses

of systemic CCK-8 induce *c-fos* expression in the vagal termination field: the nucleus of the solitary tract (NTS), an area that also includes the A₂ noradrenergic cell group, as well as area postrema (AP), lateral parabrachial nucleus (IPBN), sensory parts of the dorsal vagal complex (DMX), the locus ceruleus (LC), the subceruleus nucleus (SC), the paraventricular nucleus of the hypothalamus (PVN), supraoptic nuclei (SON), and central nucleus of the amygdala (9, 35). Catecholaminergic neurons within the A₁ and A₂ cell groups express Fos after systemic CCK-8 (24, 25). Of those cells that contain the rate-limiting enzyme in catecholamine synthesis, tyrosine hydroxylase (TH), and express Fos in response to CCK-8, some project to the supraoptic hypothalamus and may mediate secretion of oxytocin in response to CCK-8 (38). However, most NTS cells activated by CCK-8 are not noradrenergic, and these cells remain largely uncharacterized.

Several reports have suggested that the effects of CCK-8 are mediated via norepinephrine (NE) (17, 18, 31, 32, 37), dopamine (2–5), and/or serotonin (10, 41, 42, 48). In the present study, we tested the hypothesis that NE is necessary for satiety induced by peripheral CCK-8.

METHODS

All experiments were conducted in accordance with protocols approved by the University of Washington Animal Care Committee. Mice congenitally deficient in dopamine β-hydroxylase (DβH) were produced as previously described (52). Heterozygous littermates were used as controls because they have normal levels of NE and epinephrine (51). Mice were housed in Plexiglas cages with cob bedding and a cotton nestlet block in a temperature-controlled room with a 12:12-h light/dark cycle. They were maintained on pelleted mouse breeder diet (Lab diet 5015, Test Diet, Richmond, IN) that has a slightly higher fat content (25% of calories from fat) than standard mouse diet. CCK-8 (Sigma, St. Louis, MO) was dissolved in sterile PBS at room temperature and administered by intraperitoneal injection in a volume of 0.01 ml/g body wt. Doses were counterbalanced.

Experiment 1. Six DβH-deficient (*Dbh*^{-/-}) and eight heterozygous (*Dbh*^{+/-}) male mice were used. Mice were housed

Address for reprint requests and other correspondence: C. M. Cannon, Dept. of Biochemistry, Howard Hughes Medical Institute, Univ. of Washington, Seattle WA 98195-7370 (E-mail: caesia@u.washington.edu).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

individually and because *Dbh*^{-/-} mice are cold sensitive (53), all cages were arranged so that 50% of the cage floor was over a heating pad. A thermometer left in an empty cage with the tip over the heated section registered 26°C. Most mice chose to make their nests on the heated side and, rather than sleeping curled, were often found sprawled belly down on a spot of Plexiglas cleared of shavings. This was especially true of the knockouts.

Mice were each given three doses (4, 8, and 16 µg/kg body wt) of CCK-8, and PBS was given as control. These doses were chosen based on prior experience with CCK in mice, as well as reports within the literature that suggest mice are less sensitive to a given dose of CCK than are rats (30). We attempted to train the mice to drink sucrose at a regular time each day, but the mice showed sporadic interest after 2 wk, so the mice were fasted before being tested with CCK to motivate them to consume. Metabolic rate in mice is sensitive to ambient temperature, and we found that mice kept on the heating pads had very mild hyperphagia after a 24-h fast. However, significant hyperphagia was observed after 48 h without food. The level of hyperphagia produced by this protocol was comparable to that observed in mice of this size after a 24-h fast at ambient room temperature, and the mice were not observed to be abnormally voracious. At the start of the 48-h fast, food was removed in the late afternoon and mice were given a clean cage with fresh bedding. Because mice become significantly hyperphagic on days when fresh chow is added to the cage, food removed from each cage was individually bagged and returned to the same cage at the end of the fast. On testing days, mice were weighed in the late afternoon and then injected with CCK-8 or PBS. Chow was immediately returned to the overhead hopper. Chow was removed and weighed at 0.5, 1, 24, and 48 h after return of the food. Body weight was measured daily.

Data were analyzed for the 0.5- and 1-h intervals separately from the 24- and 48-h intervals. Each set was analyzed by three-way repeated-measures ANOVA using Statistica. The factors used in the three-way analysis were dose, time, and genotype.

Experiment 2. In *experiment 1*, mice responded to all doses of CCK with significant hypophagia, so the present experiment was conducted to include lower doses that may have a less pronounced effect on intake. Thirteen *DBH*-deficient (*Dbh*^{-/-}, mean body weight 23.83 ± 1.48 g) and twelve heterozygous (*Dbh*^{+/-}, 19.34 ± 0.70 g) female mice were used. Mice were housed in groups of four or five in cages containing two or three *Dbh*^{-/-} and two *Dbh*^{+/-}. After a fast of 24 h, mice were removed from the home cage, weighed, and injected. Immediately after injection, each mouse was transferred to a familiar Plexiglas testing cage containing three pellets of weighed chow, cob bedding, and ad libitum access to water. Mice were observed during the testing period for behavioral signs of nausea (elongation of the body, gaping, raising the tail, and lowering the belly to the floor), ataxia, sedation, and anxiety (locomotion within the cage, avoidance of the front of the cage). Mice did not exhibit any of the above signs and spent the majority of time eating, drinking, grooming, or exploring the cage. Chow was removed and weighed at 0.5 and 1 h, when mice were returned to their home cage. Mice were given ad libitum access to chow for 3 or more days between tests. Data were analyzed as described for *experiment 1*.

RESULTS

Experiment 1. CCK reduced deprivation-induced cumulative food intake in a dose-dependent manner in

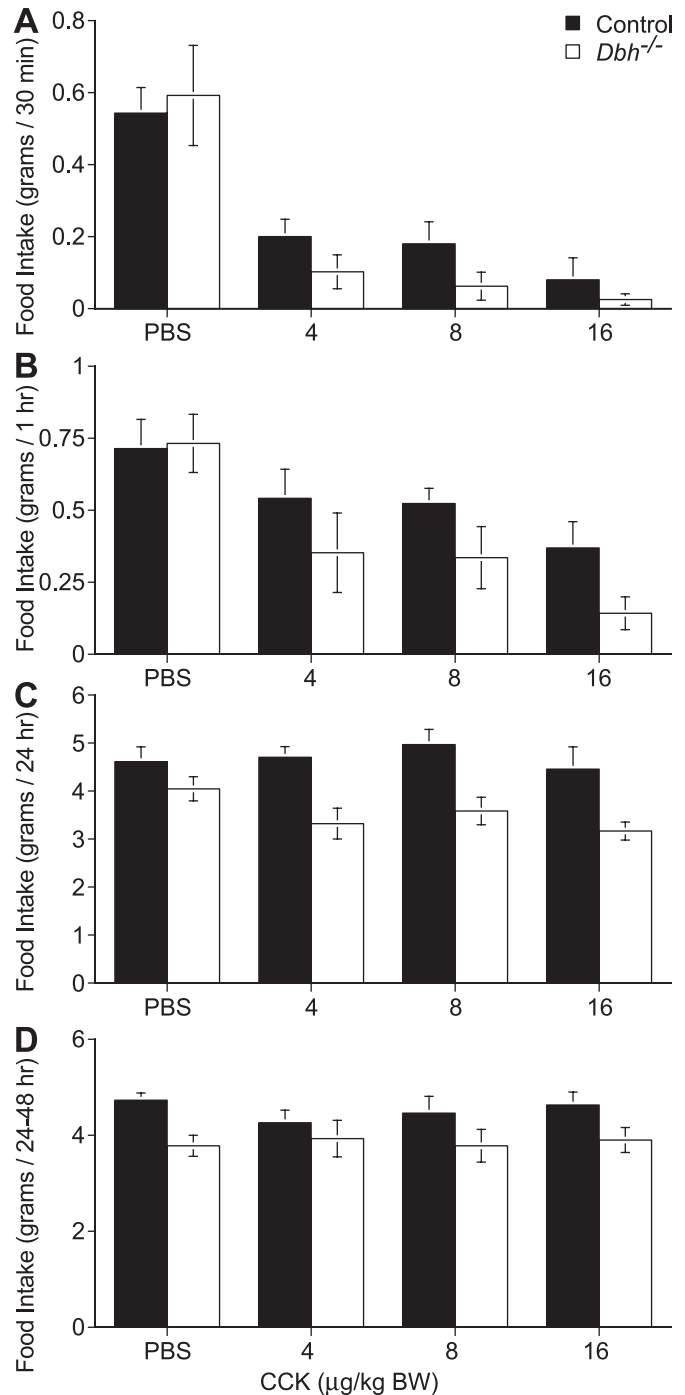


Fig. 1. CCK-8 reduced the deprivation-induced intake of male *Dbh*^{-/-} mice. Intake of mice (cumulative grams ± SE) was measured 30 min (A), 1 (B), 24 (C), and 48 h (D) after a 48-h fast. CCK-8 reduced food intake in a dose-dependent manner in both *Dbh*^{-/-} mice and *Dbh*^{+/-} controls within the first hour ($F_{3,36} = 37.15$, $P < 0.01$) (A and B). There was a trend toward greater reduction of feeding in the *Dbh*^{-/-} mice, although this did not reach significance ($F_{3,36} = 1.7$, $P = 0.18$). At 24 and 48 h after CCK, there was no significant effect of dose ($F_{3,36} = 0.77$, $P = 0.52$) or time ($F_{1,12} = 0.36$, $P = 0.56$) on food intake (C and D). There was a significant effect of feeding in the *Dbh*^{-/-} mice, although this did not reach significance ($F_{1,12} = 10.23$, $P < 0.01$), with the smaller *Dbh*^{-/-} mice eating less than controls. *Dbh*^{+/-} littermates were used as controls; they have normal levels of norepinephrine (NE) and epinephrine (Epi). BW, body wt.

Table 1. Body weight during a 48-h fast and subsequent recovery in *Dbh*^{+/-} and *Dbh*^{-/-} mice

	Before Fast	24-h Fasted	48-h Fasted	24-h Refed	48-h Refed
<i>Dbh</i> ^{+/-}	46.72 ± 1.36	43.74 ± 1.3	42.09 ± 1.3	45.57 ± 1.33	45.62 ± 1.32
<i>Dbh</i> ^{-/-}	32.96 ± 1.07	30.97 ± 1.03	29.68 ± 1.02	31.72 ± 0.98	32.08 ± 0.99

Values are mean weight across treatment conditions (g ± SE).

both *Dbh*^{-/-} and *Dbh*^{+/-} littermates within the first hour ($F_{1,12} = 59.07$, $P < 0.01$; Fig. 1, A and B). There was a trend toward greater reduction of feeding in the *Dbh*^{-/-} mice, although this did not reach significance ($F_{1,12} = 1.29$, $P = 0.28$). Despite smaller body size (Table 1), *Dbh*^{-/-} mice were equally capable of hyperphagia after a fast. Mice continued to eat throughout the hour, so that there was also a significant effect of time ($F_{1,12} = 69.00$, $P < 0.01$), although the interaction between time and genotype was not significant ($F_{1,12} = 2.51$, $P = 0.14$).

At 24 and 48 h after CCK, there was no significant effect of dose ($F_{1,12} = 0.77$, $P = 0.52$) or time ($F_{1,12} = 0.36$, $P = 0.56$) on food intake. There was a significant effect of genotype ($F_{1,12} = 10.23$, $P < 0.01$), with the smaller *Dbh*^{-/-} mice eating less than *Dbh*^{+/-} littermates. It was previously reported that *Dbh*^{-/-} mice have elevated metabolic rate and decreased feed efficiency (53). In other words, under basal conditions, *Dbh*^{-/-} mice eat less than *Dbh*^{+/-} littermates when total intake is compared, but when intake is normalized to body weight, *Dbh*^{-/-} mice eat more per gram body weight than *Dbh*^{+/-} littermates.

There was no significant effect of dose on body weight (data not shown). When body weight values were averaged across the four treatment conditions, *Dbh*^{+/-} and *Dbh*^{-/-} mice lost 10% of the prefast body weight after 48 h and regained weight similarly (Table 1).

Experiment 2. CCK reduced food intake in a dose-dependent manner in both *Dbh*^{-/-} and *Dbh*^{+/-} littermates within the first hour ($F_{1,23} = 407.41$, $P < 0.01$) (Fig. 2, A and B). There was a significant effect of genotype on food intake ($F_{1,23} = 21.43$, $P < 0.01$); *Dbh*^{-/-} mice had greater hyperphagia in response to a fast. As in the previous experiment, there was no significant interaction between genotype and dose of CCK ($F_{1,23} = 1.01$, $P = 0.41$); CCK attenuated intake similarly in both *Dbh*^{-/-} and *Dbh*^{+/-} mice.

DISCUSSION

The present data contradict the hypothesis that NE is necessary for the satiating effects of CCK.

Central NE was first implicated in the initiation of feeding by Grossman (15, 16), who determined that microgram quantities of NE, introduced into the hypothalamus, rapidly elicited feeding in satiated rats. Grossman's observations have been supported by subsequent findings (6, 7, 21, 23). However, the entire NE content of the rat brain, 6 nmol (39), is much less than the smallest dose effective at eliciting feeding. Of this total brain NE, the estimated size of the "functional" compartment of readily releasable NE is only 20–35%

(13, 14, 50). In addition, the smallest doses necessary to initiate feeding in satiated animals have been reported to elicit signs of discomfort, such as vocalization and ataxia (44).

Further studies refined the putative role of NE based on adrenergic receptor subtype (α vs. β) and location (medial vs. lateral hypothalamus) (21–23). Although high doses of agonists were used, these studies also demonstrated the effect of adrenergic antagonists on deprivation-induced feeding. An α -adrenergic antagonist, phentolamine, reduced deprivation-induced feeding when injected into the VMH. On the other hand, a β -adrenergic antagonist, propranolol, actually enhanced intake in deprived rats when injected into the medial or lateral hypothalamus. Leibowitz (21) proposed that endogenous NE reduces feeding when it acts at β -adrenergic receptors within the lateral hypothalamus (LH), but enhances feeding at α -adrenergic receptors within the ventromedial hypothalamus (VMH). In addition, endogenous NE release in the preoptic and anterior hypothalamus may play an im-

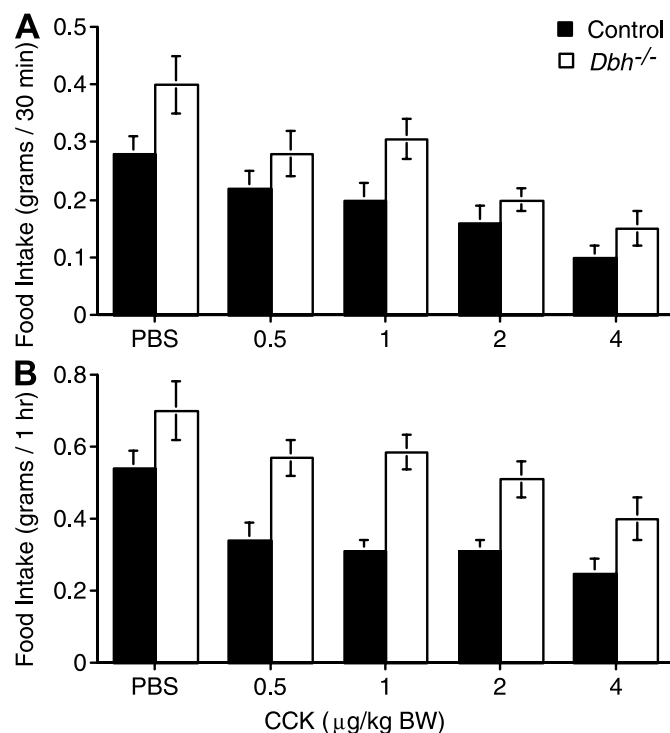


Fig. 2. Low doses of CCK-8 reduced the deprivation-induced intake of female *Dbh*^{-/-} mice. Intake of mice (cumulative grams ± SE) was measured 30 min (A) and 1 h (B) after a 24-h fast. CCK-8 reduced food intake in a dose-dependent manner in both *Dbh*^{-/-} mice and *Dbh*^{+/-} controls within the first hour ($F_{1,23} = 407.41$, $P < 0.01$). *Dbh*^{+/-} littermates were used as controls; they have normal levels of NE and Epi.

portant role in sustaining a meal, once initiated. Deprivation-induced feeding and lever pressing for food is accompanied by an elevated release of endogenous NE in this area (26, 32, 34), and doses of NE closer to the physiological range (1.48, 0.74, or 0.37 nmol) in these areas potentiated spontaneously initiated feeding by >200% (44, 46).

Feeding induced by intrahypothalamic NE (2.5 µg) is attenuated by systemic CCK-8 (37). An increased release of NE has been documented in the whole hypothalamus during either feeding or treatment with peripheral, satiating doses of CCK (17, 18). Because the effect of NE on feeding is site specific, these results are difficult to interpret. Because CCK-8 inhibits feeding, if NE plays a role in CCK-8-induced satiety, one might expect that CCK would cause increased NE release in the LH, where NE acts to reduce intake. One might also expect diminished release in the VMH and/or anterior hypothalamus, where NE can stimulate feeding or increase meal size and duration, respectively. However, in microdialysis experiments, Myers and McCaleb (36, 37) found just the opposite: peripheral CCK-8 in sated rats increased NE release in the VMH and preoptic area and diminished release in the LH. The authors concluded that "endogenous CCK interacts functionally with a pathway of noradrenergic neurons responsible for initiating satiety, or with those neurons that activate a feeding response." However, these results contradict the noradrenergic hypothesis of CCK-induced satiety as detailed above.

The chronic loss of NE did not have an appreciable effect on responding to CCK. However, the present data cannot rule out the possibility that NE and/or epinephrine may play a marginal role in the response to CCK. In addition, it is possible that compensation for the chronic lack of NE has occurred. For example, transient interference with NE signaling could affect CCK action but with chronic interference, compensatory changes could result in normal responses. Lack of NE during fetal development is lethal (52), and mothers must be treated with the synthetic precursor L-threo-3,4-dihydroxyphenylserine (DOPS) for *Dbh*^{-/-} mice to be born. DOPS is converted by the enzyme aromatic acid decarboxylase to NE directly, thus bypassing DBH. In the present study, *Dbh*^{-/-} mice were never given DOPS after birth. It is possible that the *Dbh*^{-/-} mice developed, in the absence of postnatal NE, some compensatory processes not present in normal mice. In addition, because DA is the precursor of NE, *Dbh*^{-/-} mice release DA rather than NE from their noradrenergic terminals. This "ectopic dopamine" may contribute to the unusual phenotype of these mice, although it is not clear at this time that it does. Most phenotypic characteristics of *Dbh*^{-/-} mice can be rescued by treatment with DOPS that restores NE levels to some degree while presumably leaving ectopic dopamine intact (52, 53). In this instance, there is no phenotype to reverse and it is difficult to assess whether compensation for chronic NE deficiency has occurred. However, barring the possibility of compensation for chronic loss of NE, we conclude on the basis of the

present results and the literature cited here (17, 18, 31, 32, 37), that NE is not important for CCK-induced satiety.

The authors thank J. E. Roberts for technical assistance. C. M. Cannon is the recipient of the Poncin Fellowship.

REFERENCES

1. **Barrachina MD, Martinez V, Wang L, Wei JY, and Tache Y.** Synergistic interaction between leptin and cholecystokinin to reduce short-term food intake in lean mice. *Proc Natl Acad Sci USA* 94: 10455–10460, 1997.
2. **Bednar I, Carrer H, Qureshi GA, and Sodersten P.** Dopamine D1 or D2 antagonists enhance inhibition of consummatory ingestive behavior by CCK-8. *Am J Physiol Regul Integr Comp Physiol* 269: R896–R903, 1995.
3. **Bednar I, Forsberg G, Linden A, Qureshi G, and Sodersten P.** Involvement of dopamine in inhibition of food intake by cholecystokinin octapeptide in male rats. *J Neuroendocrinol* 3: 491–496, 1991.
4. **Bednar I, Qureshi G, and Sodersten P.** A comparison between the effect of cholecystokinin octapeptide and apomorphine on ingestion of intraorally administered sucrose in male rats. *J Neuroendocrinol* 4: 727–734, 1992.
5. **Bednar I, Qureshi G, and Sodersten P.** Evidence that release of dopamine in the brain is involved in the inhibitory effect of cholecystokinin octapeptide on ingestion of intraorally infused sucrose in male rats. *J Neuroendocrinol* 4: 735–741, 1992.
6. **Booth DA.** Localization of the adrenergic feeding system in the rat diencephalon. *Science* 158: 515–517, 1967.
7. **Booth DA.** Mechanism of action of norepinephrine in eliciting an eating response on injection into the rat hypothalamus. *J Pharmacol Exp Ther* 160: 336–348, 1968.
8. **Broberger C, Holmberg K, Kuhar MJ, and Hokfelt T.** Cocaine- and amphetamine-regulated transcript in the rat vagus nerve: a putative mediator of cholecystokinin-induced satiety. *Proc Natl Acad Sci USA* 96: 13506–13511, 1999.
9. **Day HE, McKnight AT, Poat JA, and Hughes J.** Evidence that cholecystokinin induces immediate early gene expression in the brainstem, hypothalamus and amygdala of the rat by a CCKA receptor mechanism. *Neuropharmacology* 33: 719–727, 1994.
10. **Esfahani N, Bednar I, Qureshi GA, and Sodersten P.** Inhibition of serotonin synthesis attenuates inhibition of ingestive behavior by CCK-8. *Pharmacol Biochem Behav* 51: 9–12, 1995.
11. **Figlewicz DP, Sipols AJ, Seeley RJ, Chavez M, Woods SC, and Porte D Jr.** Intraventricular insulin enhances the meal-suppressive efficacy of intraventricular cholecystokinin octapeptide in the baboon. *Behav Neurosci* 109: 567–569, 1995.
12. **Gibbs J, Young R, and Smith G.** Cholecystokinin decreases food intake in rats. *J Comp Physiol Psychol* 84: 488–495, 1973.
13. **Glowinski J.** Some characteristics of the "functional" and "main storage" compartments in central catecholaminergic neurons. *Brain Res* 62: 489–493, 1973.
14. **Glowinski J.** Some new facts about synthesis, storage and release processes of monoamines in the central nervous system. In: *Perspectives in Neuropharmacology: A Tribute to Julius Axelrod*, edited by Snyder S. Toronto: Oxford Univ. Press, 1972, p. 349–403.
15. **Grossman SP.** Direct cholinergic and adrenergic stimulation of hypothalamic mechanisms. *Am J Physiol* 202: 872, 1962.
16. **Grossman SP.** Eating or drinking elicited by direct adrenergic or cholinergic stimulation of hypothalamus. *Obes Res* 5: 291–293, 1997.
17. **Kadar T, Varszegi M, Sudakov SK, Penke B, and Telegdy G.** Changes in brain monoamine levels of rats during cholecystokinin octapeptide-induced suppression of feeding. *Pharmacol Biochem Behav* 21: 339–344, 1984.
18. **Kaneyuki T, Morimasa T, and Shohmori T.** Action of peripherally administered cholecystokinin on monoaminergic and GABAergic neurons in the rat brain. *Acta Med Okayama* 43: 153–159, 1989.

19. **Kissileff HR, Pi-Sunyer FX, Thornton J, and Smith GP.** C-terminal octapeptide of cholecystokinin decreases food intake in man. *Am J Clin Nutr* 34: 154–160, 1981.
20. **Kopin AS, Mathes WF, McBride EW, Nguyen M, Al-Haider W, Schmitz F, Bonner-Weir S, Kanarek R, and Beinborn M.** The cholecystokinin-A receptor mediates inhibition of food intake yet is not essential for the maintenance of body weight. *J Clin Invest* 103: 383–391, 1999.
21. **Leibowitz SF.** Hypothalamic beta-adrenergic “satiety” system antagonizes an alpha-adrenergic “hunger” system in the rat. *Nature* 226: 963–964, 1970.
22. **Leibowitz SF.** Ingestion in the satiated rat: role of alpha and beta receptors in mediating effects of hypothalamic adrenergic stimulation. *Physiol Behav* 14: 743–754, 1975.
23. **Leibowitz SF.** Reciprocal hunger-regulating circuits involving alpha- and beta-adrenergic receptors located, respectively, in the ventromedial and lateral hypothalamus. *Proc Natl Acad Sci USA* 67: 1063–1070, 1970.
24. **Luckman S.** Fos-like immunoreactivity in the brainstem of the rat following peripheral administration of cholecystokinin. *J Neuroendocrinol* 4: 149–152, 1992.
25. **Luckman SM, Hamamura M, Antonijevic I, Dye S, and Leng G.** Involvement of cholecystokinin receptor types in pathways controlling oxytocin secretion. *Br J Pharmacol* 110: 378–384, 1993.
26. **Martin GE and Myers RD.** Evoked release of [¹⁴C]norepinephrine from the rat hypothalamus during feeding. *Am J Physiol* 229: 1547–1555, 1975.
27. **Matson CA, Reid DF, Cannon TA, and Ritter RC.** Cholecystokinin and leptin act synergistically to reduce body weight. *Am J Physiol Regul Integr Comp Physiol* 278: R882–R890, 2000.
28. **Matson CA, Reid DF, and Ritter RC.** Daily CCK injection enhances reduction of body weight by chronic intracerebroventricular leptin infusion. *Am J Physiol Regul Integr Comp Physiol* 282: R1368–R1373, 2002.
29. **Matson CA and Ritter RC.** Long-term CCK-leptin synergy suggests a role for CCK in the regulation of body weight. *Am J Physiol Regul Integr Comp Physiol* 276: R1038–R1045, 1999.
30. **Matson CA, Wiater MF, Kuijper JL, and Weigle DS.** Synergy between leptin and cholecystokinin (CCK) to control daily caloric intake. *Peptides* 18: 1275–1278, 1997.
31. **McCaleb ML and Myers RD.** Cholecystokinin acts on the hypothalamic “noradrenergic system” involved in feeding. *Peptides* 1: 47–49, 1980.
32. **McCaleb ML, Myers RD, Singer G, and Willis G.** Hypothalamic norepinephrine in the rat during feeding and push-pull perfusion with glucose, 2-DG, or insulin. *Am J Physiol Regul Integr Comp Physiol* 236: R312–R321, 1979.
33. **McMinn JE, Sindelar DK, Havel PJ, and Schwartz MW.** Leptin deficiency induced by fasting impairs the satiety response to cholecystokinin. *Endocrinology* 141: 4442–4448, 2000.
34. **McQueen A, Armstrong S, and Singer G.** Noradrenergic feeding system in monkey hypothalamus is altered by localized perfusion of glucose, insulin, 2-DG and eating. *Pharmacol Biochem Behav* 5: 491–494, 1976.
35. **Monnikes H, Lauer G, and Arnold R.** Peripheral administration of cholecystokinin activates c-fos expression in the locus coeruleus/subcoeruleus nucleus, dorsal vagal complex and paraventricular nucleus via capsaicin-sensitive vagal afferents and CCK-A receptors in the rat. *Brain Res* 770: 277–288, 1997.
36. **Myers RD.** Peptide-catecholamine interaction: feeding and satiety. *Psychopharmacol Bull* 21: 406–411, 1985.
37. **Myers RD and McCaleb ML.** Peripheral and intrahypothalamic cholecystokinin act on the noradrenergic “feeding circuit” in the rat’s diencephalon. *Neuroscience* 6: 645–655, 1981.
38. **Onaka T, Luckman SM, Antonijevic I, Palmer JR, and Leng G.** Involvement of the noradrenergic afferents from the nucleus tractus solitarius to the supraoptic nucleus in oxytocin release after peripheral cholecystokinin octapeptide in the rat. *Neuroscience* 66: 403–412, 1995.
39. **Palkovits M, Brownstein M, Saavedra JM, and Axelrod J.** Norepinephrine and dopamine content of hypothalamic nuclei of the rat. *Brain Res* 77: 137–149, 1974.
40. **Perrone MH.** Biochemical evidence that L-glutamate is a neurotransmitter of primary vagal afferent nerve fibers. *Brain Res* 230: 283–293, 1981.
41. **Poeschla B, Gibbs J, Simansky KJ, Greenberg D, and Smith GP.** Cholecystokinin-induced satiety depends on activation of 5-HT1C receptors. *Am J Physiol Regul Integr Comp Physiol* 264: R62–R64, 1993.
42. **Poeschla B, Gibbs J, Simansky KJ, and Smith GP.** The 5-HT1A agonist 8-OH-DPAT attenuates the satiating action of cholecystokinin. *Pharmacol Biochem Behav* 42: 541–543, 1992.
43. **Riedy CA, Chavez M, Figlewicz DP, and Woods SC.** Central insulin enhances sensitivity to cholecystokinin. *Physiol Behav* 58: 755–760, 1995.
44. **Ritter R.** *Noradrenergic Control of Spontaneous Meal Size in the Rat* (Thesis). University of Pennsylvania, 1974.
45. **Ritter RC, Covasa M, and Matson CA.** Cholecystokinin: proofs and prospects for involvement in control of food intake and body weight. *Neuropeptides* 33: 387–399, 1999.
46. **Ritter RC and Epstein AN.** Control of meal size by central noradrenergic action. *Proc Natl Acad Sci USA* 72: 3740–3743, 1975.
47. **Smith GP, Jerome C, Cushin BJ, Eterno R, and Simansky KJ.** Abdominal vagotomy blocks the satiety effect of cholecystokinin in the rat. *Science* 213: 1036–1037, 1981.
48. **Stallone D, Nicolaidis S, and Gibbs J.** Cholecystokinin-induced anorexia depends on serotonergic function. *Am J Physiol Regul Integr Comp Physiol* 256: R1138–R1141, 1989.
49. **Sykes RM, Spyer KM, and Izzo PN.** Demonstration of glutamate immunoreactivity in vagal sensory afferents in the nucleus tractus solitarius of the rat. *Brain Res* 762: 1–11, 1997.
50. **Thierry AM, Blanc G, and Glowinski J.** Further evidence for the heterogeneous storage of noradrenaline in central noradrenergic terminals. *Naunyn Schmiedeberg Arch Pharmacol* 279: 255–266, 1973.
51. **Thomas SA, Marck BT, Palmiter RD, and Matsumoto AM.** Restoration of norepinephrine and reversal of phenotypes in mice lacking dopamine beta-hydroxylase. *J Neurochem* 70: 2468–2476, 1998.
52. **Thomas SA, Matsumoto AM, and Palmiter RD.** Noradrenaline is essential for mouse fetal development. *Nature* 374: 643–646, 1995.
53. **Thomas SA and Palmiter RD.** Thermoregulatory and metabolic phenotypes of mice lacking noradrenaline and adrenaline. *Nature* 387: 94–97, 1997.
54. **West DB, Fey D, and Woods SC.** Cholecystokinin persistently suppresses meal size but not food intake in free-feeding rats. *Am J Physiol Regul Integr Comp Physiol* 246: R776–R787, 1984.