Effects of peripheral CCK receptor blockade on food intake in rats

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Reidelberger, Roger D., Daniel A. Castellanos, and Martin Hulce. Effects of peripheral CCK receptor blockade on food intake in rats. Am J Physiol Regul Integr Comp Physiol 285: R429–R437, 2003. First published May 8, 2003; 10.1152/ajpregu.00176.2003.—Type A cholecystokinin receptor (CCKAR) antagonists differing in blood-brain barrier permeability were used to test the hypothesis that satiety is mediated, in part, by CCK action at CCKARs located peripheral to the blood-brain barrier. At dark onset, non-food-deprived rats received a bolus injection of devazepide (2.5 μmol/kg iv), a 3-h infusion of A-70104 (1 or 3 μmol·kg⁻¹·h⁻¹ iv), or vehicle either alone or coadministered with a 3-h infusion of CCK-8 (10 nmol·kg⁻¹·h⁻¹ iv) or a 2-h intragastric infusion of peptone (1 g/h). Food intake was determined from continuous computer recordings of changes in food bowl weight. Devazepide penetrates the blood-brain barrier; A-70104, the dicyclohexylammonium salt of 1-dipentylamide (A-65186), does not. CCK-8 inhibited 3-h food intake by more than 50% and both A-70104 and devazepide abolished this response. A-70104 and devazepide stimulated food intake and similarly attenuated the anorexic response to intragastric infusion of peptone. Thus endogenous CCK appears to act, in part, at CCKARs peripheral to the blood-brain barrier to inhibit food intake. CCK is a peptide that is found throughout the brain and in neurons and endocrine cells of the gastrointestinal tract. Studies demonstrating that type A CCK receptor (CCKAR) antagonists stimulate food intake in a variety of species provide compelling evidence that CCK plays an essential role in producing the satiation that occurs with ingestion of a meal (7, 11, 12, 20, 27, 34). The popular hypothesis is that CCK, secreted from endocrine cells in the upper small intestine in response to duodenal delivery of nutrients, acts through local, paracrine stimulation of intestinal vagal sensory neurons to inhibit food intake. This hypothesis is supported by studies demonstrating the existence of CCK-secreting endocrine cells in the epithelium of the upper small intestine (8, 40), CCKARs within vagal afferent nerves (28, 45), activation of intestinal vagal afferent neurons by exogenous and endogenous CCK (13, 16, 24), and similar attenuation by CCKAR antagonists and vagal neural lesions of anorexic responses to exogenous CCK and nutrient administration (36).

Several lines of evidence suggest that this mechanism is not the only one by which CCK produces satiety. For example, we and others demonstrated that systemic administration of the CCKAR antagonist devazepide can increase food intake in rats whether or not they are vagotomized (30) or pretreated with capsaicin to lesion visceral sensory nerves (37). Furthermore, CCKAR antagonists that do not readily cross the blood-brain barrier [2-naphthalenesulphonyl-L-aspartyl-2-(phenethyl)-amide (22) and A-70104 (44)] have been reported to have no effect on food intake in rats (18, 19) and pigs (5, 21) when administered systematically under the same conditions in which devazepide, a CCKAR antagonist that readily penetrates the blood-brain barrier, stimulates food intake (19, 20). These results suggest that endogenous CCK can act at CCKARs within brain sites protected by the blood-brain barrier to produce satiety. This conclusion is further supported by studies showing that food intake releases hypothalamic CCK (14, 38), site-specific injections of CCK into the brain inhibit food intake (9), and brain injections of CCK antisera (15) and CCK receptor antagonists (17, 39) stimulate food intake.

Baldwin et al. (6) argued that peripheral CCK is not likely to be an important satiety factor because systemic administration of CCKAR antagonists that do not cross the blood-brain barrier fails to increase food intake. However, if peripheral CCK is but one of several redundant satiety signals produced by a specific meal, then blockade of peripheral CCK action may have little if any effect on intake of that meal, and it would therefore be inappropriate under these circumstances to single out the CCK signal as being unimportant. There is considerable evidence to indicate that food intake can trigger a cascade of satiety signals emanating from the mouth, stomach, small intestine, liver, and pancreas. Previous work suggests that masking of a CCK satiety signal by other satiety signals may vary with meal size and composition. In rats, the anorexia produced by duodenal delivery of specific macronutrients appears to be more sensitive to reversal by CCKAR antagonists at lower nutrient delivery rates.

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This is consistent with the idea that CCK plays an essential role in mediating the anorexia produced by the lower delivery rates and that larger delivery rates produce a greater stimulation of redundant CCK-independent satiety mechanisms.

We recently provided evidence using A-70104, a CCKAR antagonist that does not penetrate the blood-brain barrier (44), that endogenous CCK can act at CCKARs peripheral to the blood-brain barrier to inhibit food intake (32). We showed that in sham-feeding rats, intravenous infusion of A-70104 attenuates the anorexia produced by duodenal infusions of peptone, maltose, and Intralipid. In contrast, Ebenezer and Parrott (18, 21) reported that bolus intravenous injection of A-70104 has no effect on food intake in pigs or rats at doses that block the anorectic response to a bolus injection of CCK-8. It may be that A-70104 was effective in our sham-feeding rats receiving duodenal nutrient infusions because less redundancy in satiety signaling occurs when ingested liquid food rapidly drains from a gastric cannula. On the other hand, A-70104 may have been ineffective in the studies of Ebenezer and Parrott because the bolus doses administered may not have been sufficient to attenuate the satiety effects of a prolonged meal-induced secretion of endogenous CCK, despite being able to block the anorexic response to a bolus injection of CCK-8. To obviate this concern in our sham-feeding study, A-70104 was administered by continuous intravenous infusion throughout the feeding period.

The aim of the present study was to use CCKAR antagonists differing in blood-brain barrier permeability (devazepide penetrates; A-70104 does not) to determine whether endogenous CCK acts by an essential mechanism at CCKARs peripheral to the blood-brain barrier to produce satiety in real-feeding rats. An initial series of experiments determined the effects of intravenous administration of devazepide and A-70104 on the anorectic response to intravenous infusion of CCK-8 during the early dark period in non-food-deprived rats. Subsequent experiments of similar design determined the effects of intravenous administration of devazepide and A-70104 on food intake and on the anorectic response to intragastric infusion of peptone, a potent stimulus of intestinal CCK secretion. A final experiment determined the effects of bolus intravenous injections of tritiated devazepide and A-70104 on blood clearance patterns of the two compounds to assess whether bolus administration of A-70104 is sufficient to attenuate the satiety effects of a prolonged meal-induced secretion of endogenous CCK.

METHODS

Subjects. Male rats (Sasco Sprague-Dawley, Charles Rivers Lab., Kingston, NY; ~350 g at the start of the study) were housed individually in hanging wire mesh cages in a temperature-controlled room with a 12:12-h light-dark cycle (lights off at 1600). The animals were provided rat chow (Purina #5001, 3.3 kcal/g) and water ad libitum. The Animal Studies Subcommittee of the Omaha VA Medical Center approved the experimental protocol. Animal experimentation was conducted in conformity with the “Guiding Principles for Research Involving Animals and Human Beings” of the American Physiological Society (1).

Surgical procedures. The procedures for implantation of a gastric cannula for peptone infusion, a jugular vein catheter for administration of CCKAR antagonists and CCK-8, and an abdominal aortic catheter for blood collection were described previously (2, 41). Gastric, jugular vein, and aortic cannulas were filled with either water or heparinized saline (40 U/ml), plugged with stainless steel wire, and flushed every other day to maintain patency. Cannulas of rats used in feeding experiments were connected to 40-cm lengths of tubing passed through a protective spring coil connected between a lightweight saddle (IITC, Woodland Hills, CA) worn by the rat and either a single- or double-channel infusion swivel (Instech Laboratories, Plymouth Meeting, PA). The double-channel swivel permitted simultaneous administration of CCKAR antagonist intravenously and peptone intragastrically.

Effects of devazepide and A-70104 on CCK-8-induced inhibition of food intake. This series of experiments established doses of A-70104 and devazepide that can block the effects of a large inhibitory dose of CCK-8 on food intake. The dose-response effects of CCK-8 on food intake were determined previously (31). Three experiments were performed. The first determined the effects of bolus intravenous injection of devazepide (2.5 μmol/kg) on feeding and on the anorectic response to intravenous infusion of CCK-8 (10 nmol-kg⁻¹-h⁻¹). The second and third experiments determined the effects of continuous intravenous infusion of A-70104 (1 and 3 μmol-kg⁻¹-h⁻¹) and devazepide (10 nmol-kg⁻¹-h⁻¹). Devazepide was administered by bolus injection because it has a relatively long plasma half-life of ~4 h (Dr. J. Lin, Merck Sharpe & Dohme, unpublished data). The half-life of A-70104 had not previously been determined. A-70104 was therefore administered by continuous infusion to ensure blockade of CCKARs during the first 3 h of the feeding period.

Animals were permitted at least 1 wk to recover from surgery. They were then tethered to infusion swivels and adapted to experimental conditions for at least 1 wk before the start of experiments. Excess amounts of fresh ground rat chow were provided each day at 1300. Non-food-deprived rats received a bolus intravenous injection of devazepide (2.5 μmol/kg = 1 mg/kg, 1 ml/kg; Merck Sharpe & Dohme Research Laboratories) or vehicle (5% DMSO, 5% Tween 80, 90% 0.15 M NaCl) 15 min before receiving a 3.25-h intravenous infusion of CCK-8 (10 nmol-kg⁻¹-h⁻¹, 3 ml/h; Research Plus, Bayonne, NJ) or vehicle (0.15 M NaCl, 0.1% BSA), which began 15 min before dark onset. Food intake during the first 17 h after dark onset was determined, as described previously, from continuous computer recordings of changes in food bowl weight (41). Infusions were administered using a syringe infusion pump (PHD2000, Harvard Apparatus, South Natick, MA); pumps were turned on and off by a computer program. Each rat (n = 14) received each treatment in random order at intervals of at least 48 h. At the end of an experiment, data from a rat were excluded if its jugular vein catheter was not patent. A catheter was deemed to be patent if the rat lost consciousness within 10 s of a bolus injection of the short-acting anesthetic brevital into the catheter. A-70104 experiments were identical in design except rats received a 3.5-h intravenous infusion of A-70104 (1 or 3 μmol·kg⁻¹·h⁻¹, 3 ml/h) or vehicle (0.15 M NaCl, 0.1% BSA, 1% DMSO) beginning 15 min before onset of the CCK-8 or vehicle infusion.
The development and characterization of A-70104 as a CCKAR antagonist have been described previously (3, 4, 10, 23). Two batches of A-70104 were used in these studies. One was provided by Dr. James Kerwin, Jr. (Abbott Laboratories, Abbott Park, IL); the other was synthesized by Dr. Martin Hulce as previously described (25). Briefly, (R)-N,N-dipentyl N,N-(3-quinolinolyl)glutamic acid amide (A-65186) was prepared from (R)-γ-benzyl- N-BOC-glutamic acid, dipentylamine, and 3-quinolinocarboxylic acid in four steps and 38% overall chemical yield. The dicyclohexylammonium salt of A-65186 (A-70104) was prepared from A-65186 and dicyclohexylamine in 98% chemical yield. In aqueous solution, A-70104 is chemically identical to A-65186. Chromatography, nuclear magnetic resonance, and mass spectrometry were employed to demonstrate that the compound was identical to that provided by Dr. James Kerwin, Jr.

Effects of devazepide and A-70104 on food intake. Preparation of animals and design of experiments were similar to those described above for the effects of devazepide and A-70104 on CCK-8-induced inhibition of food intake. Eight experiments were performed to determine the effects of different doses of A-70104 on food intake and to assess the reproducibility of feeding responses to devazepide and A-70104. Two experiments used two different groups of rats to determine the effects of bolus intravenous injection of devazepide (2.5 μmol/kg) 15 min before dark onset on food intake in non-food-deprived animals. The other five experiments used four different groups of rats to determine the effects of a 3.25-h intravenous infusion of A-70104 (1 and 3 μmol·kg⁻¹·h⁻¹) beginning 15 min before dark onset on food intake in non-food-deprived animals. Two experiments determined the effects of the lower dose of A-70104 in two different groups of rats and three experiments determined the effects of the higher dose of A-70104 in two different groups of rats. Within an individual experiment, each rat received vehicle and a single dose of either devazepide or A-70104 in random order on days separated by at least 48 h. Previous work demonstrated that devazepide is less effective in stimulating food intake in animals that already have a significant drive to eat. With the use of data from within the individual experiments, we plotted the relationship between an animal’s baseline food intake (response to vehicle administration) during the first 3 h after dark onset and its response to devazepide or A-70104 administration (increase above its baseline intake) during the same 3-h period. The final experiment compared the effects of devazepide (2.5 μmol/kg), A-70104 (3 μmol·kg⁻¹·h⁻¹), and vehicle administration on food intake in rats receiving a 2-h intragastric infusion of peptone (1 g/h, 4 ml/h; EZMix tryptone, Sigma) beginning 15 min before dark onset. For each experiment, treatments were administered to groups of 14 to 16 rats.

Blood clearance patterns for devazepide and A-70104. Rats with jugular vein and abdominal aortic catheters were permitted at least 1 wk to recover from surgery. They were then adapted to experimental conditions for at least 1 wk before the start of experiments, which included light restraint in a Bollman-type cage and intravenous injection of saline. Rats were deprived of food for ~17 h before experiments. Three rats received a bolus intravenous injection (1 ml/kg) of devazepide (2.5 μmol/kg) containing [³H]devazepide (10 μCi/ml, 73.9 Ci/mmol; New England Nuclear Life Sciences Products, Boston) and the three rats received a bolus injection of A-70104 (0.5 μmol/kg) containing [³H]A-65186 (10 μCi/ml, 92 Ci/mmol (25)). Blood samples (0.5 ml) were collected from the aortic catheter into heparinized tubes at multiple times postinjection (from 0.5 to 360 min). An equal volume of heparinized saline was injected intravenously following the collection of each sample. Plasma was separated from red blood cells by centrifugation and transferred to a scintillation vial containing 10 ml of scintillation fluid (Ultima Gold, Packard Instrument, Meriden, CT). [³H] activity was measured using a Packard 1600 TR scintillation counter. One milliliter of tissue solubilizer (Amershams NCS-II) was added to the red blood cell pellet, and the mixture was vortexed and incubated overnight at 45°C. Twenty microliters of the solubilized pellet were then added to a scintillation vial containing 10 ml of scintillation fluid and 30 μl of glacial acetic acid, and [³H] activity was measured.

Statistical analyses. Values are presented as group means ± SE. Our intent was not to compare data across experiments. Thus data from each experiment were analyzed separately. Effects of devazepide and A-70104 on feeding, CCK-8-induced inhibition of feeding, and intragastric peptide-induced inhibition of feeding were evaluated using a within-subjects repeated-measures ANOVA. Planned comparisons of treatment means were evaluated by direct contrasts of means using the computer program SYSTAT. Differences between means were considered significant when P < 0.05. A one-tailed test was used for postulated unidirectional effects. The relationship between 3-h baseline food intake (X) and percent change in 3-h food intake (Y) produced by either devazepide or A-70104 was approximated with the exponential equation

\[ Y = a e^{-bX} \]

using nonlinear regression analysis to estimate parameters a and b. The method of Moodings et al. (26) was used to compare the relationships for devazepide and A-70104.

RESULTS

Effects of devazepide and A-70104 on CCK-8-induced inhibition of food intake. Figure 1A shows the individual and combined effects of a bolus intravenous injection of devazepide (2.5 μmol/kg) and a 3.25-h intravenous infusion of CCK-8 (10 nmol·kg⁻¹·h⁻¹) at dark onset on food intake. CCK-8 alone produced a significant, sustained reduction in cumulative food intake across the 17-h test period, with a peak inhibition of 64% at 3 h (P < 0.001), decreasing to 23% inhibition by 17 h (P < 0.001). Devazepide alone produced a significant, sustained increase in cumulative food intake across the 17-h period, with a peak stimulation of 39% at 3 h (P < 0.01), decreasing to 12% stimulation by 17 h (P < 0.05). Devazepide completely abolished the anorexie response to CCK-8. Cumulative intakes at all time points in animals receiving devazepide and CCK-8 were not different from those observed at the same time points in the same animals receiving devazepide alone.

Figure 1B shows the individual and combined effects of 3-h intravenous infusions of A-70104 (1 μmol·kg⁻¹·h⁻¹) and CCK-8 (10 nmol·kg⁻¹·h⁻¹) at dark onset on food intake. CCK-8 alone produced a significant, sustained reduction in cumulative food intake across the 17-h test period, with a peak inhibition of 77% at 3 h (P < 0.001), decreasing to 17% inhibition by 17 h (P < 0.01). A-70104 alone did not significantly affect cumulative food intake at any time across the 17-h period. A-70104 completely abolished the anorexie response to CCK-8 after the first hour of coadmi-
tion. Cumulative intakes at all times after the first hour in animals receiving A-70104 and CCK-8 were not different from those observed at the same time points in the same animals receiving A-70104 alone.

Fig. 1. Effects of intravenous administration of devazepide (2.5 μmol/kg; A and B, respectively) on food intake in 13–14 rats. Non-food-deprived rats received a bolus intravenous injection of devazepide or vehicle beginning 15 min before dark onset. Food intake was during the first 17 h after dark onset. *P < 0.05, †P < 0.01, and ‡P < 0.001 compared with response at the same time to vehicle administration.

Fig. 1C shows the individual and combined effects of 3-h intravenous infusions of a threefold higher dose of A-70104 (3 μmol·kg⁻¹·h⁻¹) and CCK-8 (10 nmol·kg⁻¹·h⁻¹) at dark onset on food intake. CCK-8 alone produced a significant, sustained reduction in

Fig. 2. Effects of intravenous administration of devazepide (2.5 μmol/kg; A and B, respectively) on food intake in 13–14 rats. Non-food-deprived rats received a bolus intravenous injection of devazepide or vehicle beginning 15 min before dark onset. Food intake was during the first 17 h after dark onset. *P < 0.05, †P < 0.01, and ‡P < 0.001 compared with response at the same time to vehicle administration.
cumulative food intake across the 17-h test period, with a peak inhibition of 76% at 1 h ($P < 0.05$), decreasing to 14% inhibition by 17 h ($P < 0.01$). A-70104 alone did not significantly affect cumulative food intake at any time across the 17-h period. A-70104 completely abolished the anorexic response to CCK-8. Cumulative intakes at all time points in animals receiving A-70104 and CCK-8 were not different from those observed at the same time points in the same animals receiving A-70104 alone.

Effects of devazepide and A-70104 on food intake. Figure 2, A and B, shows the effects of a bolus intravenous injection of devazepide (2.5 $\mu$mol/kg) at dark onset on food intake in separate experiments with different groups of rats. Figure 2A shows that devazepide produced a significant, sustained increase in cumulative food intake for 6 h, with a peak stimulation of 55% at 1 h ($P < 0.05$), decreasing to 18% stimulation by 6 h ($P < 0.05$). Figure 2B shows that devazepide produced a significant, sustained increase in cumulative food intake across the 17-h test period, with a peak stimulation of 41% at 2 h ($P < 0.01$), decreasing to 16% stimulation by 17 h ($P < 0.01$).

Figure 3, A and B, shows the effects of a 3.25-h intravenous infusion of A-70104 (1 $\mu$mol·kg$^{-1}$·h$^{-1}$) at dark onset on food intake in separate experiments with different groups of rats. A-70104 had no significant effect on food intake in either experiment. Figure 3, C-E, shows the feeding effects of a threefold higher dose of A-70104 (3 $\mu$mol·kg$^{-1}$·h$^{-1}$) in three separate experiments with two different groups of rats. A-70104 increased food intake in each experiment, although the amplitude and timing of the effect varied across experiments. Figure 3C shows that A-70104 produced a significant increase in cumulative food intake from 2 to 5 h after onset of A-70104 infusion, with a peak stimulation of 28% at 2 h ($P < 0.01$), decreasing to 14% stimulation by 5 h ($P < 0.05$). Figure 3D shows that A-70104 produced a significant, transient increase in cumulative food intake of ~15% ($P < 0.05$) 3 h after
Cumulative food intake of A-70104 produced a significant onset of A-70104 infusion. Figure 3E shows that A-70104 produced a significant, transient increase in cumulative food intake of ~10% (P < 0.05) 7 h after onset of A-70104 infusion.

Nonlinear regression analysis revealed a highly significant inverse relationship between baseline food intake in a rat during the first 3 h of the dark period and the ability of devazepide to increase food intake during the same period in the same rat (Y = 618e⁻⁰.⁶⁶X, r² = 0.58, P < 0.001; Fig. 4A). The stimulatory effect of A-70104 on 3-h food intake was similarly related to baseline intake (Y = 548e⁻⁰.⁵⁰X, r² = 0.49, P < 0.001; Fig. 4B). The relationship for A-70104 was not statistically different from that of devazepide (P > 0.05).

However, average baseline food intake across the multiple experiments was larger in rats receiving A-70104 compared with devazepide [6.4 ± 2.0 vs. 5.0 ± 1.7 g, respectively, F(1,129) = 52, P < 0.001], which is the likely reason for the smaller, inconsistent stimulatory effect of A-70104 on food intake across the multiple experiments.

The last experiment determined the effects of bolus intravenous injection of devazepide (2.5 μmol/kg) and a 3.5-h intravenous infusion of A-70104 (3 μmol·kg⁻¹·h⁻¹) at dark onset in rats receiving a 2-h intragastric infusion of peptone (1 g/h) to reduce voluntary intake and stimulate endogenous CCK secretion. Figure 5 shows that devazepide produced a significant, sustained increase in cumulative food intake from 2 to 17 h, with a peak stimulation of 155% at 2 h (P < 0.05), decreasing to 16% stimulation at 17 h (P < 0.01). A-70104 produced a significant, sustained increase in cumulative food intake from 2 to 5 h, with a peak stimulation of 220% at 1 h (P < 0.05), decreasing to 24% stimulation at 5 h (P < 0.05).

**Blood clearance patterns for devazepide and A-70104.** Bolus intravenous injection of A-70104 (0.5 μmol/kg, 1 ml/kg) containing a trace amount of [³H]A-65186 (10 μCi/ml) produced a 10-fold higher [³H] activity in whole blood collected 0.5 min postinjection than that observed following administration of a fivefold higher dose of devazepide (2.5 μmol/kg, 1 ml/kg) containing a trace amount of [³H]devazepide (10 μCi/ml) (Fig. 6A). For each compound, blood [³H] activities then rapidly decreased to a relatively constant level of ~10,000 dpm/ml by 20 min, which was sustained for more than 3 h. Changes in plasma [³H] activity following [³H]A-65186 injection were nearly identical to those observed during the experiment. The solid line depicts a highly significant fit of the data to an exponential equation (devazepide: Y = 618e⁻⁰.⁶⁶X, r² = 0.58, P < 0.001; A-70104: Y = 548e⁻⁰.⁵⁰X, r² = 0.49, P < 0.001).
in whole blood (Fig. 6, A and B). In contrast, plasma $^3$H activity rapidly declined during the first hour following injection of devazepide to a level that was nearly 25% of that observed in whole blood. Thereafter, plasma $^3$H activity increased nearly threefold to a relatively stable level of ~6,000 dpm/ml of blood.

**DISCUSSION**

CCKAR antagonists with different blood-brain barrier permeabilities [devazepide penetrates (29, 44), A-70104 does not (44)] were used to test the hypothesis that satiety is mediated, in part, by an essential CCK action at CCKARs located peripheral to the blood-brain barrier. If this hypothesis were true, intravenous administration of either antagonist should stimulate food intake. We previously determined that intravenous administration of A-70104 and devazepide attenuates the anorexia produced by duodenal infusions of peptone, maltose, and Intralipid in sham-feeding rats (32). The present study demonstrates that both antagonists also increase chow intake in non-food-deprived, real-feeding rats during the early dark period. We previously determined that immunoneutralization of circulating CCK has no effect on food intake under the same experimental conditions (35). Together, these results suggest that endogenous CCK acts by an essential paracrine and (or) neurocrine mechanism at CCKARs peripheral to the blood-brain barrier to inhibit food intake.

It was not the intent of the present study to compare the effects of A-70104 and devazepide on food intake to assess whether blockade of CCKARs throughout the body produces a different effect on feeding than does blockade of only peripheral CCKARs. Only single doses of A-70104 and devazepide were tested in our experiments. A meaningful comparison of the effects of A-70104 and devazepide would require that multiple doses of each antagonist be evaluated. Only then could A-70104 and devazepide potencies and efficacies be determined and compared in a statistically rigorous manner.

Our results show that CCKAR blockade is less able to stimulate food intake during the early dark period in non-food-deprived rats that tend to eat a relatively large amount of food during this period. In general, rats used in the A-70104 experiments ate more food during the early dark period than those used in the devazepide experiments. This likely explains why A-70104 was less consistent in stimulating food intake across the multiple experiments. In a subsequent experiment, we directly compared the effects of single doses of devazepide and A-70104 in rats receiving an intragastric infusion of peptone to decrease voluntary intake and to stimulate endogenous CCK secretion. Each CCKAR antagonist stimulated food intake similarly and more robustly than when administered in the absence of peptone infusion.

In contrast to our results, Ebenezer and Parrot reported that systemic administration of A-70104 has no effect on food intake in pigs (21) and rats (18). Bolus intravenous injection of A-70104 at doses that blocked the anorexic response to a bolus intravenous injection of CCK-8 had no effect on food intake. Under the same conditions, bolus intravenous injection of devazepide increased food intake (18, 20). If A-70104 has a relatively short half-life, the bolus doses of A-70104 used in these studies may not have been sufficient to significantly attenuate the satiety effects of a prolonged meal-induced secretion of endogenous CCK, despite being able to block the anorexic response to a bolus injection of CCK-8. On the other hand, devazepide’s ability to stimulate food intake when given by bolus injection may have been because it has a relatively long plasma half-life of ~4 h. To obviate this concern in our
This conclusion is supported by studies showing that CCK may also act as a neurotransmitter or neuromodulator within two different brain regions to produce satiety, one region that includes the nucleus of the solitary tract in the hindbrain and another more distributed region within the medial-basal hypothalamus.

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REFERENCES


DISCLOSURES

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