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A-71623, a Selective CCK-A Receptor Agonist, Suppresses Food Intake in the Mouse, Dog, and Monkey

K. E. ASIN,[1] L. BEDNARZ, A. L. NIKKEL, P. A. GORE, JR. AND A. M. NADZAN

Abbott Laboratories, Division of Neurological Sciences, Dept. 47H, Bldg. AP10, Abbott Park, IL 60064

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ASIN, K. E., L. BEDNARZ, A. L. NIKKEL, P. A. GORE, JR. AND A. M. NADZAN. *A-71623, a selective CCK-A receptor agonist, suppresses food intake in the mouse, dog, and monkey.* PHARMACOL BIOCHEM BEHAV 42(4) 699-704, 1992.—The anorectic actions of cholecystokinin (CCK)-8 and of a selective CCK-A agonist, A-71623, were examined in CD1 mice, beagle dogs, and cynomolgous monkeys. A-71623 suppressed intakes in all species tested, and the effects were blocked by a selective CCK-A antagonist, A-70104. In the dog only, CCK-8 was more potent on a molar basis compared to A-71623, although the effects of both CCK agonists were more short-lived in the dog compared to the other species tested. Our results support other evidence suggesting that the anorectic actions of exogenous application of CCK-8 in these species are mediated via stimulation of the CCK-A receptor subtype.

Cholecystokinin A-71623 CCK-A CCK-B Feeding Species comparisons A-70104 Anorectics

SYSTEMIC injections of cholecystokinin (CCK)-8 have been reported to suppress food intake in a wide variety of species, including the pig, dog, cat, monkey, rat, mouse, and man (1,3,6,7,8,12,13). Since CCK-8 has affinity for both the CCK-A and CCK-B (or gastrin) receptor subtypes (14), it has been difficult in the past to specify the neuronal substrates of the response. However, the recent availability of selective receptor antagonists has permitted some analysis of the receptors involved, and studies indicate that stimulation of the CCK-A receptor by exogenous CCK-8 administration underlies the anorectic activity of this compound (3,4).

We recently reported (2) that a CCK-4 analog, A-71623, has high affinity and selectivity for the CCK-A receptor, making it a valuable tool for studying directly the role of this receptor. A-71623 potently suppresses food intakes when administered to rats and has improved duration of action compared to CCK-8 (2). Since the actions of A-71623 in the rat were at least as pronounced as those as CCK-8 following IP administration, we sought to examine the effects of this selective CCK-A agonist on the feeding behavior across time in mice, dogs, and cynomolgous monkeys. To confirm the pharmacologic specificity of these effects, we also studied the ability of a selective CCK-A antagonist, A-70104, the dicyclohexylammonium salt of A-65186 (11), to attenuate the anorectic actions of A-71623 in these species.

METHOD

Mice

Subjects were 40 naive, male, CD1 mice, supplied by Charles River, weighing approximately 30–35 g upon arrival from the supplier. Animals were individually housed in hanging wire mesh cages and were maintained on a 12 L : 12 D cycle. Mice were allowed free access to chow for several days after their arrival, during which time they were presented with approximately 15 ml of a liquid diet (Ensure™, Ross Laboratories, Columbus, OH) to reduce any neophobic tendencies to the new diet. Following this, chow was removed from the cages and animals were given access to bottles of a 60 : 40 Ensure : water solution for 60 min in the morning and 90 min in the afternoon; intakes were recorded every 15 min for the morning feeding period and at the end of the afternoon session. Once stable baselines had been achieved (about 10 days), testing was begun. On the test day, mice were divided into five groups matched for morning intakes on the previous day. Animals were injected with either A-71623 (0, 1, 3, 10, or 30 nmol/kg, IP) or CCK-8 (0, 1, 3, 10, or 30 nmol/kg, IP) approximately 10 min before the morning drinking session. Injection volumes were 10.0 ml/kg. Intakes were recorded every 15 min for 60 min. There was a 1-week interval between

[1] To whom requests for reprints should be addressed.

tests. Although afternoon intakes were recorded, no compound affected this parameter.

The ability of A-70104 to reduce the effects of A-71623 was studied in another group of mice maintained as described above. A-70104 (0 or 300 nmol/kg, IP) was injected 12 min before A-71623 (0 or 10 nmol/kg, IP), which was injected 12 min prior to the presentation of food. There were 11–12 mice in each of the four treatment groups. Intakes were recorded during the subsequent 60-min period.

Dogs

Subjects were female beagle dogs (Marshall Farms USA, Inc., North Rose, NY) weighing 8–11 kg and were maintained under conditions similar to those of Reidelberger et al. (17). Animals were singly housed and were exercised daily; water was available ad lib. Dogs were allowed access to dog chow for 20 h/day. At 9:00 a.m., the chow was removed for 4 h to ensure that a dog would not have eaten just prior to a 3-h intake measurement period, which began at 1:00 p.m. At this time, animals were presented with a gravy-style dog food (Jewel™ Co., Melrose Pk, IL) blended 1 : 1 with water to form a slurry. One-hundred grams of this mixture was combined with 400 g regular laboratory dog chow, which was then presented to each dog; intakes were recorded periodically for the next 3 h. After this time, regular dog chow was returned to the animals. A-71623 (0, 10, 30, or 100 nmol/kg, IM) or CCK-8 (0, 1, or 10 nmol/kg, IM) was administered approximately 15 min before the presentation of the mixed diet in a volume of 0.25 ml/kg using a within-subjects design. Doses were administered in a randomized order. At least 3 days intervened between tests.

The effects of A-70104 on A-71623-induced anorexia in dogs was also studied. A-70104 (600 nmol/kg, IM) was administered 10 min prior to A-71623 (30 nmol/kg, IM), which was injected 20 min before the presentation of the gravy-chow mixture.

Monkeys

Five male cynomolgus monkeys, weighing approximately 4.5–6 kg, served as subjects. Animals were singly housed with water available ad lib. While monkeys were being maintained on monkey chow, they were presented with several hundred ml of Enrich overnight. After this, animals were placed on a food-restricted diet similar to that used by others (5). On weekdays, monkeys were given access to the liquid diet for 45 min in the morning (9:00 a.m.) and for 180 min in the afternoon (1:00–4:00); intakes were recorded periodically. On weekends, animals were allowed access to Enrich™ for 180 min and were also given approximately 35 g monkey chow. After baseline intakes had stabilized, A-71623 (0, 1, 10, or 30 nmol/kg, IM) or CCK-8 (0, 1, 10, or 30 nmol/kg, IM) was administered 15 min prior to the afternoon feeding period; the injection volume was 0.5 ml/kg. Doses were administered in a counterbalanced order using a within-subjects design. Testing was conducted one to two times/week, with at least 3 days intervening between tests. Following these studies, we examined the ability of A-70104 to block the anorectic actions of A-71623 (10 nmol/kg). Using a repeated-measures design ($N = 5$), animals were given the following three treatments: a) vehicle (Veh) + Veh; b) Veh + A-71623; or c) A-70104 (600 nmol/kg, IM) + A-71623. Three of these monkeys also received A-70104 + Veh. A-70104 was administered 15 min prior to A-71623; food was presented 15 min after the agonist.

Rats

For purposes of species dose comparisons following IM drug administration, A-71623 was injected IM into rats. Subjects were adult, male Sprague-Dawley rats, weighing approximately 300 g at the time of testing. Animals were singly housed and maintained on a 12 L : 12 D schedule. Before beginning the study, all animals were given approximately 20 ml of a liquid diet (Ensure) overnight. Rat chow and water were available ad lib except food was removed 4 h prior to the daily presentation of Ensure. Animals were allowed access to Ensure for 1 h per day for approximately 12 days, by which time intakes had stabilized. On the test day, A-71623 (0, 30, 60, 100, and 300 nmol/kg) was injected (IM) into the rear flank 20 min prior to Ensure presentation. Intakes were recorded at various intervals throughout the subsequent 2-h period.

Drugs

A-71623 was administered in a 1–10% dimethyl sulfoxide (DMSO) sterile water solution, occasionally in the presence of equimolar base (NaOH). CCK-8 was dissolved in sterile water. A-70104 was prepared as a 5–10% DMSO/sterile water solution.

Statistics

Data from individual tests were analyzed using the DATA, MGLH, and STATS modules of Systat™. Noncumulative intake data for each time point were analyzed using analysis of variance (ANOVA) (see below).

RESULTS

Mice

Cumulative intakes of mice following injections of CCK-8 (0, 1, 3, 10, and 30 nmol/kg, IP) and A-71623 (0, 1, 3, 10, and 30 nmol/kg) are shown in Fig. 1. Noncumulative intake data were analyzed using a dose × time ANOVA model (with repeated measures on the time factor) with the method of contrast comparisons. The doses required to produce 50% reductions in 30- and 60-min cumulative intakes (ED_{50}s) were determined using least-squares regression analysis.

CCK-8. Analysis of absolute intake data over time indicated that following all doses of CCK-8, intakes were reduced during the first 15 min of food presentation [$F(1, 31) > 16.60$, $p < 0.003$, for all comparisons to vehicle]. During the 30- to 45-min testing period, intakes were significantly *increased* following the 10-nmol/kg dose, $F(1, 31) = 4.89$, $p < 0.04$, and also tended to be increased at this same time period following 30 nmol/kg, $F(1, 31) = 3.69$, $p < 0.064$. The 30- and 60-min ED_{50}s were approximately 25 and 100 nmol/kg, respectively.

A-71623. Statistical analysis indicated that doses of 3 and 10 nmol/kg significantly suppressed intakes relative to vehicle during the first 15 min of testing [$F(1, 31) > 37.0$, $p < 0.001$, for all comparisons]. A dose of 30 nmol/kg suppressed intakes across the first 45 min of testing [$F(1, 31) > 6.9$, $p < 0.02$, for all comparisons to vehicle]. The 10-nmol/kg dose of A-71623 significantly *increased* intakes during the last 15-min measurement period (46–60 min) relative to vehicle, $F(1, 31) = 6.21$, $p < 0.018$; intakes during this interval also tended to increase following the 30-nmol/kg dose, $F(1, 31) = 3.44$, $p < 0.74$. The 30- and 60-min ED_{50}s were 4 and 7 nmol/kg, respectively.

The effects of A-70104 on intakes are shown in Fig. 1c. A

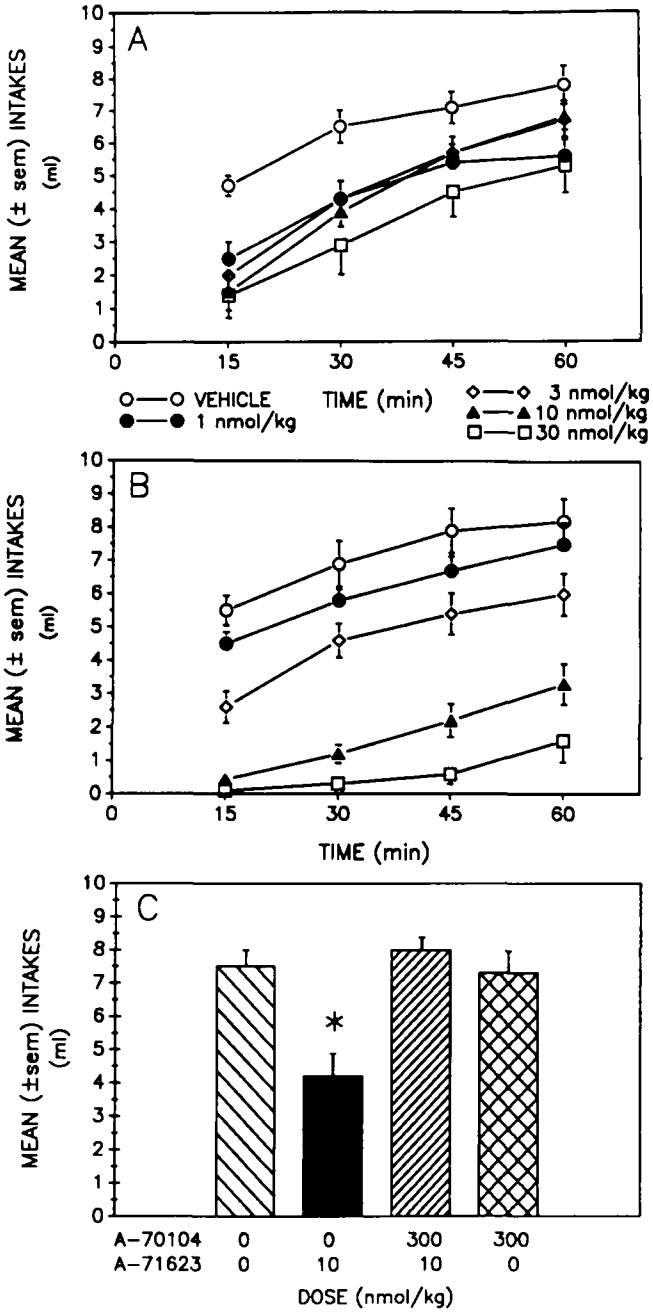

FIG. 1. Suppression of food intake over time in mice. Effects of various doses of (A) CCK-8 and (B) A-71623 on feeding. (C) The anorectic actions of A-71623 are attenuated by pretreatment with the selective CCK-A receptor antagonist A-70104. *$p < 0.01$ compared to A-70104 + A-71623.

2 × 2 (A-70104 × A-71623) ANOVA conducted on 60-min intake data indicated that A-70104 significantly attenuated the effects of A-71623, as indicated by a significant interaction term, $F(1, 41) = 5.29$, $p < 0.03$. Posthoc contrast analysis indicated that the intakes of rats treated with A-70104 + vehicle did not differ from those receiving vehicle alone [$t(21) = 0.92$].

Dogs

Cumulative intakes of nine dogs following injections of CCK-8 (0, 1, or 10 nmol/kg, IM) or A-71623 (0, 10, or 30 nmol/kg) are shown in Fig. 2. Absolute intakes following drug treatments were analyzed using two-way ANOVAs (dose × time) with repeated measures on both factors.

CCK-8. ANOVA indicated significant dose, $F(2, 16) = 4.03$, $p < 0.04$, and time, $F(4, 32) = 25.64$, $p < 0.001$, effects and a dose × time interaction, $F(8, 64) = 7.22$, $p < 0.001$. Posthoc analysis using the method of contrasts indicated that during the first 15 min of testing intakes following

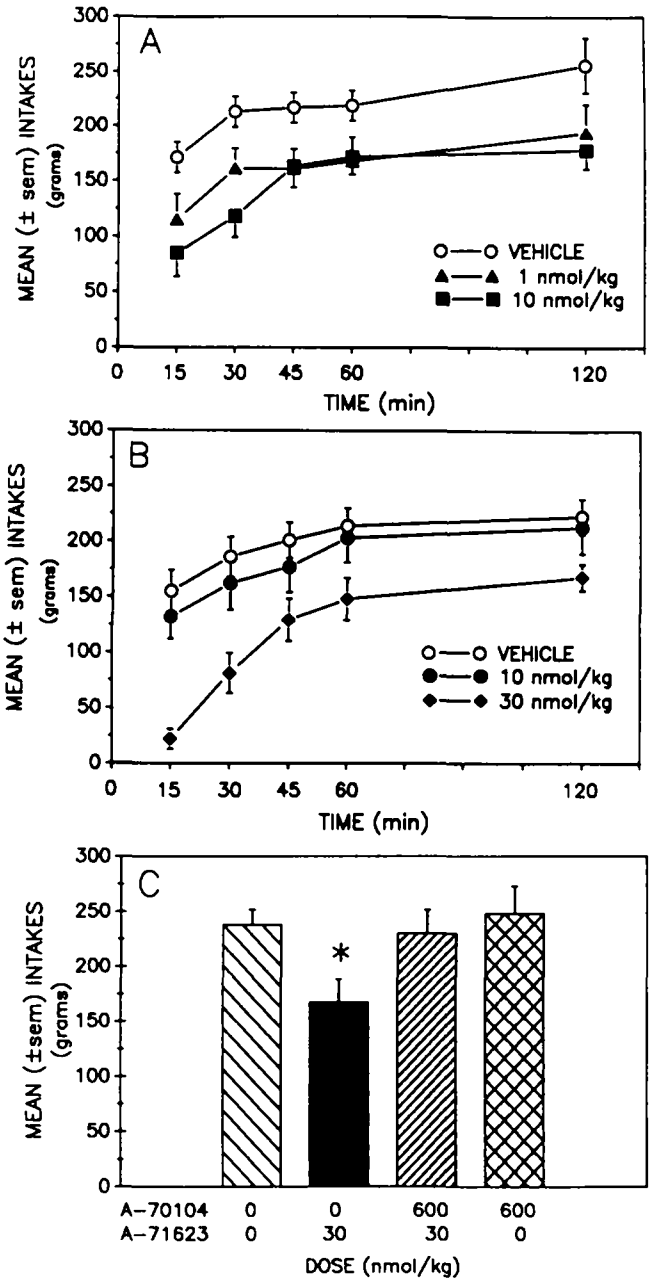

FIG. 2. Suppression of food intake over time in beagle dogs. Intakes of dog food were significantly suppressed by (A) CCK-8 and (B) A-71623. (C) The actions of A-71623 are blocked by pretreatment with A-70104. *$p < 0.02$ compared to A-70104 + A-71623.

both 1 and 10 nmol/kg were significantly lower than following vehicle [$F(1, 8) = 8.33$, $p < 0.02$, and $F(1, 8) = 23.33$, $p < 0.001$, respectively]. Intakes following 10 nmol/kg CCK-8 were significantly *greater* than following vehicle during the 30- to 45-min measurement period, $F(1, 8) = 11.79$, $p < 0.009$. No other comparisons attained significance.

A-71623. Analysis of intake data indicated significant dose, $F(2, 16) = 4.38$, $p < 0.03$, and time effects, $F(4, 32) = 30.63$, $p < 0.001$, and a significant dose × time interaction, $F(8, 64) = 11.21$, $p < 0.001$. Posthoc contrast analyses indicated that during the first 15-min testing interval intakes following 30 nmol/kg A-71623 were significantly lower than those following vehicle, $F(1, 8) = 33.19$, $p < 0.001$, whereas intakes following 10 nmol/kg were not, $F(1, 8) = 1.63$, $p < 0.24$. Intakes during the 30- to 45-min period were significantly *increased* following 30 nmol/kg compared to vehicle, $F(1, 8) = 5.71$, $p < 0.05$. No other comparisons were statistically reliable.

Since only two doses of CCK-8 and A-71623 were tested, ED_{50}s values were not determined. However, on a molar basis, CCK-8 was more potent in suppressing intakes in dogs, particularly at the earlier measurement periods, than was A-71623, as was borne out by statistical analyses (see above). A dose of 10 nmol/kg CCK-8, but not A-71623, significantly suppressed 15-min intakes.

The ability of A-70104 to antagonize the suppression of feeding produced by A-71623 is shown in Fig. 2c. A pretreatment × posttreatment ANOVA, with repeated measures on both factors, followed by contrast analysis indicated that 60-min intakes were significantly suppressed by A-71623 compared to vehicle, $F(1, 8) = 11.53$, $p < 0.009$. Furthermore, food consumption following A-70104 + A-71623 was significantly greater than that following vehicle + A-71623, $F(1, 8) = 9.11$, $p < 0.02$. A-70104 in the absence of A-71623 failed to elevate intakes compared to vehicle alone ($F < 1$).

Monkeys

The effects of CCK-8 (0, 1, 10, and 30 nmol/kg, IM) and A-71623 (0, 1, 10, and 30 nmol/kg) on cumulative intakes over time are shown in Fig. 3. Data collected over the 3-h measurement period were analyzed using 2-way ANOVAs (dose × time), with repeated measures on both factors.

CCK-8. One animal vomited within 15 min after injection of CCK-8 (30 nmol/kg). Analysis of the suppression of intakes produced by CCK-8 (0–30 nmol/kg, IM) indicated significant effects of dose, $F(3, 12) = 4.28$, $p < 0.03$, and time, $F(5, 20) = 12.80$, $p < 0.001$; the dose × time interaction term was not statistically reliable ($F < 1$). Posthoc analysis of the dose effect collapsed over time indicated that 10 and 30 nmol/kg CCK-8 significantly suppressed intakes compared to vehicle [$F(1, 4) > 10.76$, $p < 0.03$, for both comparisons]. Additional contrast analysis indicated that the effects of CCK-8 were short-lived; intakes were suppressed only during the first 15-min measurement period by the 1- and 30-nmol/kg doses [$F(1, 4) > 13.64$, $p < 0.03$, for both comparisons]. Since the dose-response curve for CCK-8 was nonlinear, the ED_{50} was not calculated.

A-71623. Analysis of intake data generated following A-71623 (0–30 nmol/kg, IM) indicated significant dose, $F(3, 12) = 42.11$, $p < 0.001$, and time, $F(5, 20) = 17.33$, $p < 0.001$, effects: the dose × time interaction did not achieve significance, $F(15, 60) = 1.36$, $p < 0.20$. Posthoc analysis of the dose effect using contrasts indicated that when the data are collapsed across time all doses of A-71623 significantly suppressed intakes compared to vehicle [$F(1, 4) > 9.67$, $p < 0.04$, for all comparisons]. The highest dose of A-71623 (30 nmol/kg) significantly suppressed intakes compared to vehicle at the 15-, 30-, 60-, 120-, and 180-min time points [$F(1, 4) > 11.76$, $p < 0.03$, for all comparisons]. Intakes were also reduced by 10 nmol/kg A-71623 compared to vehicle for the first 30 min [$F(1, 4) > 11.79$, $p < 0.03$, for both comparisons]. The 30-, 60-, 120-, and 180-min ED_{50}s were determined to be 3.7, 3.3, 4.7, and 5.7 nmol/kg, respectively.

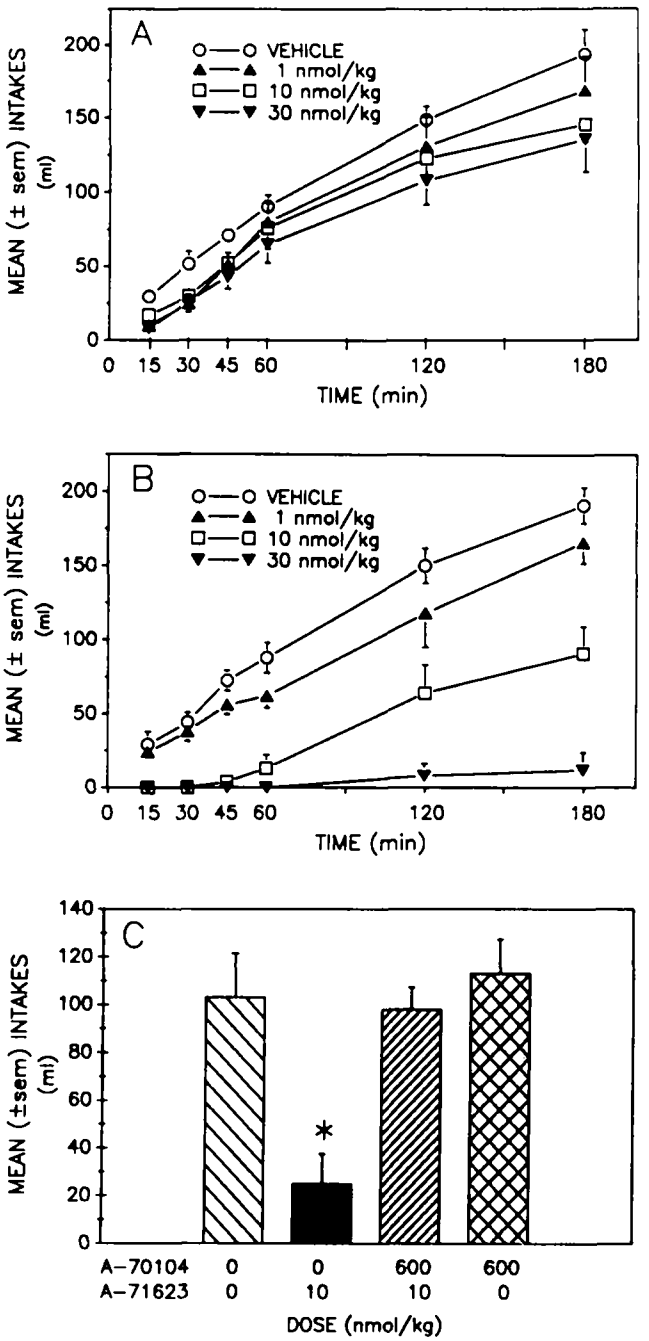

FIG. 3. Intakes of a liquid diet by monkeys treated with (A) CCK-8 and (B) A-71623. (C) The anorectic actions of A-71623 are attenuated by A-70104. *$p < 0.004$ compared to A-70104 + A-71623.

The effect of A-70104 (600 nmol/kg) on the suppression of feeding produced by A-70104 (10 nmol/kg) is shown in

Fig. 3c. Data were analyzed by the method of contrasts using a multivariate model. This analysis revealed that 60-min intakes following vehicle (Veh) + A-71623 were significantly lower than those following Veh + Veh, $F(1, 4) = 9.06$, $p < 0.04$, or A-70104 + A-71623, $F(1, 4) = 43.86$, $p < 0.004$. A paired t-test conducted on data from the three monkeys treated with A-70104 + Veh and Veh + Veh indicated that the antagonist did not enhance feeding [$t(2) < 1.0$; mean ($\pm$SEM) difference score = 10.0 + 10.0 ml].

Rat

A-71623 significantly suppressed intakes after IM administration in rats. The approximate ED_{50}s for suppressing 30- and 60-min cumulative intakes were 37.7 and 44.4 nmol/kg, respectively (data not shown).

DISCUSSION

In previous studies, we reported increased anorectic potency of A-71623 compared to CCK-8 in the rat (2). We therefore sought to expand these observations by examining the relative potencies of these compounds in other species. The results of these studies indicate that administration of A-71623, a selective CCK-A agonist, can suppress feeding behavior in mice, dogs, and monkeys.

Koopmans et al. (13) were the first to report suppression of food intake in mice following CCK-pancreozymin. Feeding was significantly reduced only during the first 15 min of testing, and a graph of their data suggests that increases in intakes were seen in some cases for mice receiving higher doses of the compound. Their results are similar to what we report here with CCK-8.

Compared to the rat (2), the effects of CCK-8 in the mouse were less pronounced and less dose dependent. Thus, the dose-response curve for CCK-8 (injected IP) in the mouse was extremely shallow, and the approximate ED_{50} for 60-min intakes was 100 nmol/kg, as opposed to 14 nmol/kg in the rat. In contrast to CCK-8, A-71623 produced dose-dependent suppressions in intakes in both the rat and mouse with 60-min ED_{50}s of approximately 4 and 7 nmol/kg, respectively. Thus, based upon ED_{50} determinations, A-71623 was approximately 6 and 14 $\times$ more potent than CCK-8 in suppressing 30- and 60-min intakes, respectively, in mice. As we reported for the rat, the anorexia seen with CCK-8 was considerably more short-lived than that of A-71623, as reflected in the relative changes in ED_{50}s over time. Our ability to block the anorectic actions of A-71623 in mice with A-70104 is consistent with other observations that the anorectic effects of CCK-8 are attenuated by the selective CCK-A antagonist MK-329 (4,18).

CCK-8 has been found to suppress intakes in beagle and mongrel dogs (8,10,17). There has also been one (negative) report on the effects of CCK-8 in timber wolves, administered IM via dart gun. In that study (15), only a single dose (1 μg/kg) was tested and animals had been deprived of food for 48 h.

There has been some question regarding a physiological role for CCK in the control of intakes in the dog. Blood levels required for suppression of intakes following exogenous CCK application far surpass endogenous plasma CCK blood levels following feeding (17). In addition, intraduodenal perfusion of fat into the dog, which stimulates pancreatic protein and gallbladder contractions via CCK release, fails to reduce sham feeding (16). In contrast, intravenous administration of MK-329 has been reported to increase feeding in prefed beagle dogs (9), suggesting a role for endogenous CCK (and concomitant stimulation of the CCK-A receptor) in feeding in this species. We failed to find a significant enhancement in intakes with A-70104 in dogs, as well as in mice and monkeys, suggesting that the effects of CCK-A antagonists may be paradigm specific.

For comparative purposes, A-71623 was tested in the rat following intramuscular administration and intakes were monitored for 2 h. The 60-min ED_{50}s generated in this species were quite similar to those generated in the dog, although in the dog the effects of A-7162 were considerably more short-lived than in the rat and monkey (see below). Levels of CCK-like immunoreactivity are similar in the dog and rat in the small intestine, although differences exist in other gut areas (19). Furthermore, the dog appears to be somewhat unique compared to other species since CCK-8 was significantly more potent in suppressing intakes than A-71623 at the same molar dose (10 nmol/kg, IM).

CCK (20 Ivy Dog U/kg) has been shown to significantly suppress food intakes in food-deprived rhesus monkeys following IV administration (6). The compound was primarily effective during the first 15 min of the 180-min feeding period. These authors also reported suppression of 15-min intakes in two monkeys following 0.91 μg/kg CCK-8. Intravenous CCK-8 has also been reported to suppress feeding in baboons (5). Using the IM route of administration, we were able to demonstrate relatively brief anorectic effects of CCK-8. On a molar basis, however, A-71623 more potently suppressed intakes in these monkeys compared to CCK-8, with an approximate 60-min ED_{50} of 6 nmol/kg. Intakes following the highest dose of A-71623 remained depressed throughout the 180-min testing period. These results are consistent with our earlier findings in the rat that despite CCK-8's relatively greater affinity for the CCK-A receptor compared to A-71623 (14) the behavioral effects of the tetrapeptide are typically longer-lived (2).

To summarize, we demonstrated the ability of a selective CCK-A receptor agonist to suppress intakes in the rat, mouse, dog, and monkey. These results suggest conservation of CCK-A receptor function across species.

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