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Receptor Mediation of the Stimulus Properties of Cholecystokinin

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MELTON, P. M. AND A. L. RILEY. *Receptor mediation of the stimulus properties of cholecystokinin.* PHARMACOL BIOCHEM BEHAV 48(1) 275-279, 1994.—Recently, Melton, Kopman, and Riley (20) reported the rapid acquisition of drug discrimination learning using the sulfated form of cholecystokinin (CCK) within the conditioned taste aversion baseline of drug discrimination learning. The present study was designed to explore the receptor mediation of the stimulus properties of CCK within this procedure. Every fourth day, experimental subjects were given CCK-saccharin-LiCl pairings, and on the intervening recovery days, saccharin alone. Once discriminative control was established, doses of the CCK receptor antagonists devazepide (CCK-type A receptor subtype) and L-365,260 (CCK-type B receptor subtype) were administered in combination with the training dose of CCK. Unlike L-365,260 (1-1000 μg/kg), devazepide (1 μg/kg) blocked the CCK stimulus, suggesting that within this design CCK's stimulus properties are mediated by the CCK-type A receptor subtype.

CCK Drug discrimination Taste aversion Antagonism Devazepide L-365,260

RECENTLY, Melton, Kopman, and Riley (20) reported the rapid acquisition of drug discrimination learning using the sulfated form of cholecystokinin (CCK) within the conditioned taste aversion baseline of drug discrimination learning (18,29). More specifically, animals injected with CCK prior to the presentation of saccharin-LiCl pairings and with the CCK vehicle prior to the presentation of saccharin alone acquired the CCK/vehicle discrimination, avoiding saccharin when it was preceded by CCK and consuming the same saccharin solution when it was preceded by the CCK vehicle (19). Although discriminative control can be established with CCK, currently little is known about its stimulus properties, for example, its similarities to opiate antagonists, emetics, adipsogenics and other gut peptides, what classes of compounds might serve as antagonists or agonists to its effects, and what specific receptor or receptors might mediate its stimulus properties.

The present study was designed to explore the latter question, specifically, the receptor mediation of the stimulus properties of CCK. Two CCK receptor subtypes have been identified and labeled type A and type B, given their predominant localization in the periphery and brain, respectively (8,10,23). Aside from location, CCK-type A and B receptors have also been differentiated in relation to functional effects. For example, type A receptors have been implicated in the satiating effect of CCK (5,22,28,33), while type B receptors have been implicated in its anxiogenic effects [panic attacks in humans and reduction in exploratory behavior of animals placed in a novel or fear-provoking environment (1,7,27,30)]. To determine the receptor subtype mediation of CCK's stimulus properties, in the present experiment animals trained to discriminate CCK from its vehicle within the taste aversion baseline of drug discrimination learning were administered selective CCK-type A (devazepide) and B (L-365,260) receptor antagonists alone and in combination with the training dose of CCK.

METHOD

Subjects

The subjects were 12 drug-naive, female rats of Long-Evans descent, approximately 250-300 g at the start of the experiment. They were housed in individual wire-mesh cages and were maintained on a 12 L : 12 D cycle (lights on at 0800 h) and at an ambient temperature of 23°C for the duration of the experiment. Subjects received restricted access to fluid for the duration of the study, but were maintained on ad lib food.

Drugs

The sulfated form of cholecystokinin octapeptide (generously supplied by the Squibb Institute) was prepared at a concentration of 10 μg/ml of distilled water and injected at a

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dose of either 3.2 or 5.6 μg/kg. Devazepide and L-365,260 (generously supplied by Merck Pharmaceuticals) were prepared at concentrations of 0.2 and 2 μg/ml and 2-2000 μg/ml, respectively, in a 5% DMSO, 5% Tween, 90% distilled water solution. Devazepide (0, 0.1, and 1 μg/kg) and L-365,260 (0, 1, 10, 100, and 1000 μg/kg) were administered alone and in combination with the 3.2 μg/kg dose of CCK.

Procedure

Phase I: acquisition. During the light phase (1500-1700 h), subjects (n = 12) were given restricted access to water for 50 consecutive days. Over this period, the duration of restricted access decreased from 20 min (days 1-24) to 10 min (days 25-35) to the terminal value of 5 min (days 36-50). On day 51, all subjects were given intraperitoneal (IP) injections of distilled water 30 min (0.50 ml/kg) and 5 min (0.56 ml/kg) prior to the 5 min access period. On days 52-54, following the two aforementioned injections of distilled water, a novel saccharin solution (0.1% w/v saccharin sodium salt, Sigma Chemical Co., St Louis, MO) replaced water during the 5 min access period (saccharin habituation). On day 55 (conditioning trial 1), all subjects were given an IP injection of distilled water (0.50 ml/kg) 30 min prior to an IP injection of CCK (5.6 μg/kg) which, in turn, was administered 5 min prior to 5 min saccharin access. Immediately following saccharin access on this day, subjects were matched on saccharin consumption and assigned to one of two groups (groups L and W, n = 6 per group). Subjects in group L were given an IP injection of 1.8 mEq/0.15 M LiCl (76.8 mg/kg), while subjects in group W were given an equivolume injection of the distilled water vehicle. Thus, the two groups were treated similarly in that all subjects were administered CCK prior to saccharin access. Only subjects in group L, however, were injected with LiCl following saccharin. On the following 3 days, all subjects were injected with distilled water 30 min and 5 min prior to saccharin access. No injections were given following saccharin access on these recovery days. This alternating procedure of conditioning (CCK-saccharin-LiCl or CCK-saccharin-distilled water) and recovery (distilled water-saccharin) was repeated for six complete cycles in all subjects. The procedure was then continued replacing the 5.6 μg/kg training dose of CCK with a 3.2 μg/kg dose, until each experimental subject consumed at least 50% less than the mean of the control subjects for three consecutive conditioning trials or until 15 conditioning/recovery cycles had been completed. To maintain body weight during the acquisition phase, all subjects received 5 min additional access to saccharin approximately 16 h after CCK injections on conditioning days.

Phase II: antagonism. The procedure during this phase was identical with that described for Phase I, with the exception that on the second recovery day following conditioning devazepide (0, 0.1, or 1 μg/kg) or L-365,260 (0, 1, 10, or 1000 μg/kg) was administered 30 min prior to the training dose of CCK (3.2 μg/kg) which, in turn, was administered 5 min prior to saccharin access. To assess the effects of devazepide and L-365,260 alone on saccharin consumption, each dose of these drugs was also administered 30 min prior to a distilled water injection (0.50 ml/kg) which, in turn, was administered 5 min prior to saccharin access. No injections followed saccharin access on any of these test sessions. An experimental subject was tested as described only if it had consumed 50% less than the mean of the control subjects on the immediately preceding conditioning trial. Doses of devazepide and L-365,260 were administered in a mixed pattern, with all subjects receiving each dose at least once. A subject received a specific dose a second time if following the first determination at this dose it consumed saccharin at control levels while other subjects in group L avoided saccharin consumption (i.e., displayed discriminative control). Under such conditions, the average of two administrations was used in graphic representation and statistical analysis. During this phase, the 5% DMSO, 5% Tween, 90% distilled water vehicle for devazepide and L-365,260 was randomly administered prior to the training dose of CCK on conditioning days. This change in procedure was implemented to reduce the possibility that the subjects would learn that the vehicle signaled that saccharin would not be paired with LiCl. To maintain body weight during antagonism testing, all subjects received 5 min additional access to saccharin approximately 16 h after CCK injections on conditioning and test days.

Statistical Analysis

A two-tailed Mann-Whitney U-test was performed on all between-group comparisons of saccharin consumption. A two-tailed Wilcoxon matched-pairs signed-ranks test (Z) was performed on all within-group comparisons of saccharin consumption over repeated trials. Absolute probabilities are presented for all comparisons. The statistical analysis of the present results relied on nonparametric statistical tests. Such tests were used because parametric tests require normally distributed population values and homogeneity of variance. Given that we could not demonstrate that the data met these requirements, the data qualified for the use of nonparametric tests.

RESULTS

Phase I: Acquisition

Figure 1 presents the mean amount (±SEM) of saccharin consumed for groups L and W during saccharin habituation

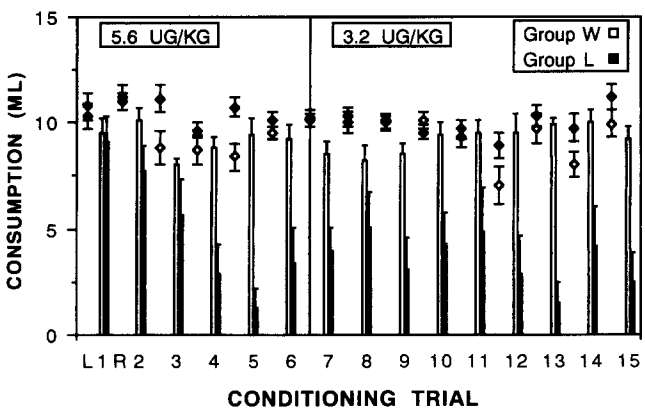

FIG. 1. Mean amount (±SEM) of saccharin consumed for subjects in groups L and W over repeated conditioning/recovery cycles. Consumption on the last day of saccharin habituation (L) is represented by filled and open diamonds for subjects in groups L and W, respectively. Consumption on each conditioning trial (i.e., following the administration of CCK) is represented by filled and open columns for subjects in groups L and W, respectively). Finally, average consumption over the three recovery sessions between each conditioning trial (R) is represented by open and closed diamonds for subjects in groups L and W, respectively. The training doses for conditioning trials 1-6 and 7-15 were 5.6 and 3.2 μg/kg, respectively.

and over 15 repeated conditioning/recovery cycles. There was no significant difference in saccharin consumption between groups L and W during saccharin habituation (U = 148, 176, p = 0.66). The mean consumption of saccharin averaged over the 3 days of saccharin habituation was 9.6 and 9.9 ml for subjects in groups L and W, respectively. On the initial conditioning trial, all subjects significantly decreased saccharin consumption compared to the last day of saccharin habituation (Z = 2.275, p = 0.02). There were no significant differences between groups on the initial conditioning trial (U = 17, 19, p = 0.87). The groups did differ in saccharin consumption on the fourth conditioning trial, at which point subjects in group L drank significantly less than subjects in group W (U = 0, 36, p = 0.004). Similar significant differences were also observed on trials 5-7, 9-10, and 12-15 (all $p < 0.05$). On the final conditioning trial of this phase, subjects in groups L and W drank 2.5 and 9.3 ml, respectively (U = 1, 35, p = 0.007). During recovery sessions, saccharin consumption for both groups remained high, approximating habituation levels.

Phase 2: Antagonism

Figure 2 illustrates the mean amount (±SEM) of saccharin consumed for subjects in groups L and W following various doses of devazepide administered in combination with distilled water or the training dose of CCK. It should be noted that antagonism functions were only determined in five of the six experimental subjects, as one subject did not maintain consistent discriminative control. As illustrated, consumption of saccharin for subjects in both groups L and W did not vary systematically over the various doses of devazepide administered in combination with the distilled water vehicle. Similarly, consumption for subjects in group W did not vary systematically over the various doses of devazepide administered in combination with the 3.2 μg/kg dose of CCK. For subjects in group L, however, there was a direct relationship between the dose of devazepide administered in combination with the training dose of CCK and the amount of saccharin consumed. With administration of the devazepide vehicle (0 μg/kg devazepide) prior to CCK, discriminative control was maintained in experimental subjects and saccharin consumption was markedly reduced (to a mean of 2.6 ml). At this dose, subjects in group L drank significantly less than subjects in group W (U = 3, 27, p = 0.03). With the administration of 0.1 μg/kg, there was no obvious loss of discriminative control by CCK in most of the experimental subjects (only one subject in group L drank at control levels, i.e., approximately 11.5 ml; the remaining subjects in group L drank between 0 and 4.75 ml). Saccharin consumption for subjects in group L, however, did not differ significantly from that for subjects in group W (U = 6, 24, p = 0.10) given the individual variability of group L at this dose. With administration of the 1 μg/kg dose of devazepide, discriminative control by CCK was lost, with all subjects in group L increasing saccharin consumption to control levels (10.9 and 10.4 ml, respectively). There was no significant difference in saccharin consumption between groups L and W at the 1 μg/kg dose of devazepide (U = 13, 17, p = 0.79). Within-group comparisons for subjects in group L demonstrated no difference in saccharin consumption after administration of the devazepide vehicle and the 0.1 μg/kg devazepide dose (Z = 0.365, p = 0.721), nor after administration of the 0.1 μg/kg devazepide dose and the 1 μg/kg devazepide dose (Z = 1.753, p = 0.080). There was a significant difference after administration of the devazepide vehicle and the 1 μg/kg devazepide dose (Z = 2.023, p = 0.043).

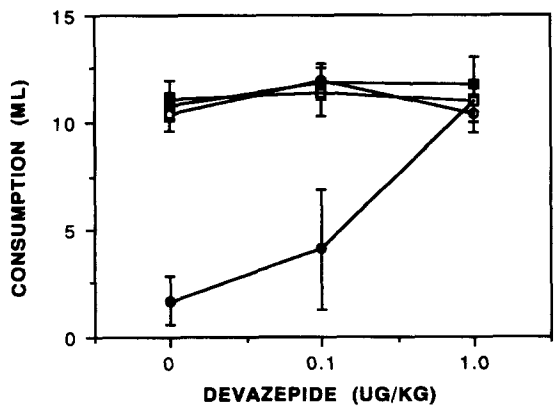

FIG. 2. Mean amount (±SEM) of saccharin consumed for subjects in groups L (filled symbols) and W (open symbols) following devazepide (0, 0.1, and 1 μg/kg) administered alone (squares) or in combination with 3.2 μg/kg CCK (circles).

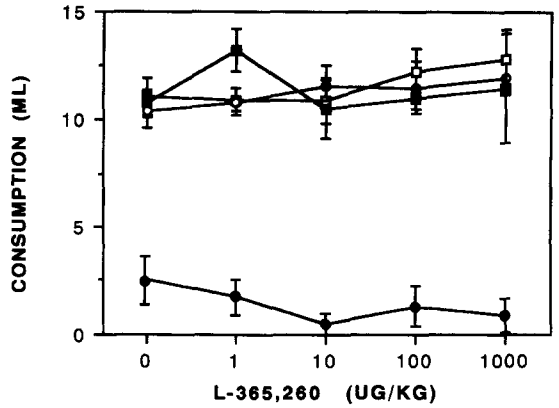

FIG. 3. Mean amount (±SEM) of saccharin consumed for subjects in groups L (filled symbols) and W (open symbols) following L-365,260 (0, 1, 10, 100, and 1000 μg/kg) administered alone (squares) or in combination with 3.2 μg/kg CCK (circles).

Figure 3 illustrates the mean amount (±SEM) of saccharin consumed for subjects in groups L and W following various doses of L-365,260 administered in combination with distilled water or the training dose of CCK (3.2 μg/kg). Again, it should be noted that antagonism functions were only determined in five of the six experimental subjects, as one subject did not maintain discriminative control. As illustrated, consumption of saccharin for subjects in both groups L and W did not vary systematically over the various doses of L-365,260 administered in combination with the distilled water vehicle. Similarly, consumption for subjects in groups W did not vary systematically over the various doses of L-365,260 administered in combination with the 3.2 μg/kg dose of CCK. Saccharin consumption for subjects in group L also did not vary systematically over the various doses of L-365,260 administered in combination with the training dose of CCK. At all doses of L-365,260 tested in combination with the 3.2 μg/kg dose of CCK, subjects in group L drank significantly less saccharin than subjects in group W (U = 3, 27, p = 0.03 at

0 μg/kg L-365,260; $U = 0, 30, p = 0.006$ for all other doses of L-365,260 tested).

DISCUSSION

Animals injected with CCK prior to saccharin-LiCl pairings and with the CCK vehicle prior to saccharin alone rapidly acquired the CCK/vehicle discrimination, avoiding saccharin when it was preceded by CCK and consuming the same saccharin solution when it was preceded by the CCK vehicle, even when the CCK training dose was reduced from 5.6 μg/kg to 3.2 μg/kg in the middle of the acquisition phase of the experiment (19,20). Although animals injected with CCK prior to the saccharin-LiCl pairings and distilled water prior to saccharin alone displayed differential consumption patterns following CCK and distilled water, it could be argued that such differences in consumption do not reflect discriminative control but reflect, instead, an interaction of CCK and LiCl, an interaction only evident in group L (group W did not receive LiCl). Specifically, it is possible that subjects receiving the CCK-saccharin-LiCl pairings decreased saccharin consumption following CCK because LiCl potentiated the unconditioned suppressant effects of CCK on saccharin consumption. Given that subjects in group W did not receive LiCl at any point in training, it is impossible from the present analysis to rule out this unconditioned effect. Although such an interaction is possible, in unpublished work from this lab animals administered CCK prior to an unpoisoned exposure to saccharin and distilled water (the CCK vehicle) prior to the saccharin-LiCl pairing acquired the drug discrimination, in this case drinking less saccharin following distilled water than following CCK. If CCK and LiCl were interacting in such a manner that LiCl potentiated the unconditioned suppressant effects of CCK, it might be expected that these subjects, too, would avoid saccharin when given CCK. Thus, the differential patterns of consumption evident in the present experiment appear to be a result of the discriminative function of CCK.

During subsequent antagonism testing, discriminative control was maintained despite the administration of a range of doses (1-1000 μg/kg) of the selective CCK-type B receptor antagonist (L-365,260) in combination with the training dose of CCK. Discriminative control by CCK was lost, however, with the administration of a relatively low dose (1 μg/kg) of the selective CCK-type A receptor antagonist (devazepide) in combination with the training dose of CCK. Given that a 1 μg/kg devazepide dose is relatively selective for the CCK-type A receptor with little if any crossover to the CCK-type B receptor (4,10,34), CCK's stimulus properties within the conditioned taste aversion baseline of drug discrimination learning appear to be mediated by the CCK-type A receptor subtype. The exclusivity of the CCK-type A receptor mediation of CCK's stimulus properties within this design is further implicated, given the lack of an effect in this experiment of doses of L-365,260 demonstrated to be effective in other designs (9,15,25).

Despite the aforementioned evidence of CCK-type A receptor mediation of the CCK stimulus, the exact nature of the CCK stimulus within the drug discrimination design has yet to be determined. More specifically, the CCK-type A receptor has been implicated in a number of diverse behavioral and physiological effects, any one of which could be descriptive of the CCK stimulus evaluated within this drug discrimination design. For example, the CCK-type A receptor has been implicated in CCK's effects on feeding (5,22,28,33) and activity (12,24). Consequently, the CCK stimulus to which animals differentially respond within this experiment could be one akin to satiety or hypolocomotion. Physiologically, the CCK-type A receptor has been implicated in an increase in plasma vasopressin (26), in increases in circulating B-endorphin concentrations (21) and plasma corticosterone (14), and in the potentiation of potassium-stimulated dopamine release from the posterior nucleus accumbens (17), to name a few. The CCK stimulus could then be one similar to a rise in vasopressin, B-endorphin, corticosterone, or dopamine. Thus, despite the increased knowledge concerning receptor subtype mediation, given the number of effects reported with CCK-type A receptor stimulation, the precise nature of the CCK stimulus within the current experimental design has yet to be determined.

In addition to a scarcity of information concerning the stimulus properties of CCK within the conditioned taste aversion baseline of drug discrimination learning, little is known about the location of the specific CCK-type A receptor population mediating the CCK stimulus. For example, there is one population of CCK-type A receptors in the nucleus of the solitary tract and in the adjacent area postrema that is accessible to circulating CCK due to the absence of an intact blood-brain barrier at that region (11,23). Blood-borne CCK may also affect a second population of abdominal CCK-type A receptors which may then affect the nucleus of the solitary tract via vagal afferents (32). It is unknown via which route activation of the CCK-type A receptors produces a discriminable CCK stimulus. Further work exploring the acquisition of drug discrimination learning with CCK under conditions of partial or total vagotomy could possibly shed light on the aforementioned question. To date, however, the location of the CCK receptor population responsible for the CCK stimulus and its route of activation remain unknown.

The generalizability of the present findings also needs to be examined in the context of the specific preparation in which the CCK discrimination was established. Specifically, female rats were administered 3.2 μg/kg CCK prior to repeated saccharin-LiCl pairings. Given that sex differences exist within taste aversion learning (3,6), it is possible that the acquisition of discriminative control (as well as its receptor mediation) would be different in male subjects. Further, given that estradiol levels are known to potentiate the effects of CCK on food (and sucrose) intake (2,16), it is possible that the different rates of acquisition for individual subjects in the present experiment (and the differential sensitivities to receptor antagonism) may have been a function of the fact that the estrous phase was not controlled. Finally, given that the training dose and the specific discrimination training procedure are known to affect both the rate of acquisition of discriminative control and the shape of generalization functions (presumably reflecting sensitivity to the discriminative effects of the training dose) (13,31), variations in these parameters are also likely to affect the discriminative stimulus properties of CCK (20). Until more work is available on the discriminative stimulus properties of CCK (both within and outside the taste aversion baseline of drug discrimination learning), the generality of its acquisition, generalization functions, and biochemical mediation will remain unknown.

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