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The inability of CCK to block (or CCK antagonists to substitute for) the stimulus effects of chlordiazepoxide

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Abstract

To further examine the relationship between cholecystokinin (CCK) and GABA, the present study assessed the ability of the CCK-A antagonist devazepide and the CCK-B antagonist L-365,260 to substitute for the stimulus effects of chlordiazepoxide (CDP), as well as the ability of CCK-8s to block these effects, in female Long–Evans rats within the conditioned taste aversion baseline of drug discrimination learning. Both devazepide and L-365,260 failed to substitute for the discriminative stimulus properties of CDP, and CCK-8s failed to block its stimulus effects. The benzodiazepine diazepam did substitute for, and the benzodiazepine antagonist flumazenil did block, the stimulus effects of CDP. This suggests that the lack of substitution for, or antagonism of, CDP by the CCK antagonists and CCK-8s, respectively, was not due to the inability of the present design to assess such effects. Possible bases for the current findings, e.g., necessity of an anxiogenic baseline, drug and receptor specificity, as well as the dose–response nature of the interaction, were discussed. Given that a relationship between CCK and GABA has been reported in other designs, the present results suggest that such a relationship may be preparation specific.

Keywords: Cholecystokinin; Devazepide; L-365,260; Chlordiazepoxide; GABA; Drug discrimination learning; Rats

1. Introduction

Given the widespread distribution of the octapeptide cholecystokinin (CCK) and its receptors throughout the CNS, it is not surprising that it has been shown to interact with a number of neurotransmitter systems, including endogenous opioid peptides (Baber et al., 1989; Dourish et al., 1990; Rady et al., 1999; Rezayat et al., 1999; Riley and Melton, 1997), hypothalamic and pituitary peptides (Hughes et al., 1991), serotonin (Bickerdike et al., 1994; Hughes et al., 1991; Kulkosky et al., 1998; Rex et al., 1994), dopamine (Acosta, 1998; Bourin et al., 1996; Crawley, 1992; Feifel et al., 1999; Hughes et al., 1991; Rasmussen, 1994) and amino acids such as glycine and aspartate (Acosta, 1998). Recent evidence also supports a reciprocal relationship between CCK and GABA, particularly the GABA/benzodiazepine receptor complex (for review, see Lydiard, 1994; van Megen et al., 1994). For example, GABA has been shown to exert a modulatory influence on CCK function (Bradwejn and de Montigny, 1984, 1985; Harro et al., 1990, 1993; Hendry et al., 1984; Rattray et al., 1993; Yaksh et al., 1987), and CCK also seems to exert a reciprocal influence on GABA function (Acosta, 1998; Pérez de la Mora et al., 1993; van Megen et al., 1996). Further, similar to the benzodiazepines diazepam (Ballaz et al., 1997; Matto et al., 1997a) and CDP (Singh et al., 1991), the CCK antagonists devazepide and L-365,260 have shown anxiolytic properties in behavioral models of anxiety (Ballaz et al., 1997; Bickerdike et al., 1994; Chopin and Briley, 1993; Daugé et al., 1989; Matto et al., 1997a). Conversely, several studies have reported anxiogenic effects of CCK-8s in similar models (Biró et al., 1997; Daugé et al., 1989; MacNeil et al., 1997; Vasar et al., 1994).

To further explore the nature of the relationship between CCK and GABA, the present study assessed the effects of the CCK-A antagonist devazepide, the CCK-B antagonist L-365,260 and CCK-8s in animals trained to discriminate the benzodiazepine CDP from its vehicle within a drug discrimination design (Järbe, 1987; Stolerman 1993). In this method, animals are trained to discriminate a drug from its vehicle. Their response to a test drug (given either alone or

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in combination with the training drug) then allows an assessment of its substitution for, or its antagonism or potentiation of, the training drug's discriminative effects (Järbe, 1987; Stolerman 1993). Accordingly, the design can assess the interaction/relationship between drugs.

In the present experiment, animals were trained to discriminate chlordiazepoxide (CDP) from its vehicle within the conditioned taste aversion baseline of drug discrimination learning (Mastropaolo and Riley, 1990; Mastropaolo et al., 1989; Melton and Riley 1993; Riley, 1995, 1997; Stevenson et al., 1992). Specifically, animals were administered CDP prior to a saccharin–LiCl pairing and the CDP vehicle prior to the presentation of saccharin alone (De Vry and Slangen, 1986; Van Hest et al., 1992; Woudenberg and Hijzen 1991). Acquisition of the drug discrimination was evidenced by the suppression of saccharin consumption following CDP administration and consumption of saccharin when it was preceded by the vehicle. Subsequently, CCK-8s and the CCK antagonists devazepide and L-365,260 were assessed for their abilities to antagonize or substitute for, respectively, the CDP training stimulus.

2. Methods

2.1. Subjects

Subjects were 19 drug-naive, female rats of Long–Evans descent, approximately 180–220 g at the start of the experiment. They were individually housed in stainless-steel wire mesh cages and maintained on a 12 L/12 D cycle (lights on at 0800 hours) and at an ambient temperature of 23°C for the duration of the experiment. Standard rat chow was available ad libitum. These same 19 animals were assessed throughout all phases of the experiment.

2.2. Drugs

CDP, generously supplied by Hoffmann-La Roche, was prepared in distilled water at a range of concentrations from 1 to 8 mg/ml and injected at doses ranging from 0.30 to 8 mg/kg (training dose). Diazepam (Sigma) was prepared in a 4% Tween 80 solution at a concentration of 1 mg/ml and injected at doses ranging from 0.10 to 3.2 mg/kg. The sulfated form of CCK octapeptide (generously supplied by Bristol-Myers Squibb) was prepared in distilled water at a concentration of 10 μg/ml and injected at doses ranging from 3.2 to 10 μg/kg. The CCK-A receptor antagonist devazepide and the CCK-B receptor antagonist L-365,260 (generously supplied by Panos Therapeutics) were suspended in a solution of 5% Tween 80, 5% DMSO and 90% distilled water at a concentration of 2 μg/ml and injected at doses of 10 and 32 μg/kg. The benzodiazepine antagonist flumazenil (generously supplied by Hoffman-La Roche) was suspended in 4% Tween 80 at a concentration of 3 mg/ml and injected at a dose of 30 mg/kg. LiCl (Sigma) was dissolved in distilled water at a concentration of 5.5 mg/ml and injected at a dose of 67.2 mg/kg. For control injections (see below), the solution in which the drug was dissolved was defined as that drug's vehicle.

2.3. Procedure

2.3.1. Phase I: acquisition

During the light phase (0800–2000 hours), subjects were given restricted access to water for 43 consecutive days. Over this period, the duration of restricted access decreased from 20 min (Days 1–3) to 10 min (Days 4–10) to the terminal value of 5 min (Days 11–43). On Days 44–46, a novel saccharin solution (0.1% w/v sodium saccharin salt, Sigma) replaced water during the 5-min access period (Saccharin Habituation) and was preceded on the last day of Saccharin Habituation by an intraperitoneal injection of distilled water at a volume of 1 ml/kg. On Day 47 (Conditioning Trial 1), all subjects were given an intraperitoneal injection of 16 mg/kg CDP 15 min before the 5-min saccharin access period. Following this injection, subjects were assigned to one of two treatment conditions, Groups Water (CW; $n = 9$) and LiCl (CL; $n = 10$), such that saccharin consumption was comparable between the two groups. Immediately following saccharin access on this day, subjects in Group CL were given an intraperitoneal injection of LiCl (67.2 mg/kg) in order to induce the aversion, while subjects in Group CW were given an equivolume injection of the distilled water vehicle. (The dose of CDP was subsequently lowered to 8 mg/kg because the initial training dose of 16 mg/kg produced generalized behavioral suppression. On all subsequent conditioning days, the dose of CDP was 8 mg/kg.) On the following 3 days, all subjects were injected with distilled water (equivolume to 8 mg/kg, 1 ml/kg) 15 min before saccharin access. No injections were given following saccharin access on these recovery days. This alternating procedure of conditioning (CDP–saccharin–LiCl or CDP–saccharin–distilled water) and recovery (distilled water–saccharin) was repeated for individual experimental subjects until discriminative control had been established (i.e., consumption by individual experimental subjects was at least 50% less than the mean of the control subjects for three consecutive conditioning trials).

2.3.2. Phase II: generalization

The procedure following the acquisition of the CDP discrimination was identical with that described above with the following exceptions. Specifically, on the second recovery day following each conditioning trial, one of a range of doses of CDP (0.30–8 mg/kg), diazepam (0.10–3.2 mg/kg), CCK (3.2–10 μg/kg), devazepide (10 and 32 μg/kg), L-365,260 (10 and 32 μg/kg) or the drugs' respective vehicles (highest volume used) replaced CDP 15 min prior to saccharin access for animals in both Groups CL and CW (see above). No injections followed saccharin access on these probe sessions. On any specific probe day, a subject

was given a drug injection only if it had consumed at least 50% less than the mean of the control group on the immediately preceding conditioning trial. Doses were administered in a mixed pattern with all subjects receiving each dose at least once. A dose was tested a second time only if there was extreme intergroup variability. Under such conditions, the average of the two administrations was used in graphic representation and statistical analyses. In order to maintain body weight during testing, subjects were given supplemental access to saccharin (approximately 10–20 ml) approximately 3 h after drug injections on conditioning and probe days.

2.3.3. Phases III and IV: antagonism with CCK and flumazenil

The procedure during these phases was identical with that described for Phase II with the exception that the subjects in Groups CL and CW were injected with CCK at 10 μg/kg immediately preceding an injection of CDP which in turn was administered 15 min prior to saccharin access. The dose of CDP was determined by finding the lowest dose at which individual animals showed discriminative control and then increasing the dose by 1/4 log to ensure discrimination. Animals were also administered CCK (10 μg/kg) followed immediately by CDP vehicle (equivolume to intermediate doses discussed above), as well as the CCK vehicle (equivolume to 10 μg/kg) immediately prior to CDP at the intermediate doses discussed above.

Animals were then injected with flumazenil at 30 mg/kg 10 min prior to an injection of CDP at 8 mg/kg, which, in turn, was administered 15 min prior to saccharin access. Animals were also administered flumazenil (30 mg/kg) followed by the CDP vehicle (equivolume to 8 mg/kg), as well as the flumazenil vehicle (equivolume to 30 mg/kg) followed by CDP (8 mg/kg) over the same time course described above.

2.4. Statistical analysis

Statements of statistical significance are based on the two-tailed Mann–Whitney U test ($P<.05$) for all between-groups comparisons of saccharin consumption. Within-groups comparisons of drug combinations were assessed using the Wilcoxon Signed-Rank test ($P<.05$), and within-groups comparisons of single drugs were assessed using the two-tailed Friedman test ($P<.05$).

3. Results

3.1. Phase I: acquisition

There were no significant differences in saccharin consumption between groups during Saccharin Habituation or over the first three conditioning trials (all P values $>.05$). On the fourth conditioning trial, subjects in Group CL drank significantly less saccharin than those in Group CW ($U=57.5$, 14.5, $P=.0360$). This difference was maintained throughout the remainder of conditioning. On the final conditioning trial of this phase, subjects in Groups CL and CW drank 4.45 and 9.33 ml of saccharin, respectively. During recovery sessions, consumption for both groups remained high, approximating habituation levels.

3.2. Phase II: generalization

Throughout this phase, data are presented for nine subjects in Group CL (one subject failed to acquire discriminative control) and nine subjects in Group CW, except where otherwise noted. Fig. 1 presents the mean amount (±S.E.M.) of saccharin consumed by subjects in Groups CL and CW following various doses of CDP, diazepam, devazepide, L-365,260 and their respective vehicles. As illustrated in Fig. 1 (top left panel), for subjects in Group CL, there was an inverse relationship between the dose of CDP and the amount of saccharin consumed (Friedman $\chi^2=36.81$, $P<.0001$). For subjects in Group CW, there were no significant changes in consumption over the increasing doses of CDP ($P>.05$). For all doses of CDP above 0.30 mg/kg, subjects in Group CL drank significantly less than subjects in Group CW (for Group CL, $n=8$ for dose of 1 mg/kg; all P values $<.05$). The top right panel of Fig. 1 presents the mean amount (±S.E.M.) of saccharin consumed by subjects in Groups CL and CW following various doses of diazepam. Data are presented for eight subjects in Group CL and nine subjects in Group CW, except where noted differently. As illustrated, for subjects in Group CL, there was an inverse relationship between the dose of diazepam and the amount of saccharin consumed, indicating the generalization of CDP's stimulus effects to those of diazepam (Friedman $\chi^2=24.34$, $P<.0001$). For subjects in Group CW, there were no significant changes in consumption over the increasing doses of diazepam ($P>.05$). For the doses of 1 (for Group CW, $n=8$) and 3.2 mg/kg, subjects in Group CL drank significantly less than subjects in Group CW ($U=8.5$, 63.5, $P=.0055$ and $U=0$, 72, $P<.0001$, respectively). The bottom left panel of Fig. 1 presents the mean amount (±S.E.M.) of saccharin consumed by subjects in Groups CL and CW following various doses of devazepide. Data are presented for eight subjects in each group, except where noted. As illustrated, there were no significant differences in consumption across the doses tested for subjects in either Group CL or Group CW (all P values>.05). For each dose tested, 0, 10 (for Group CW, $n=7$) and 32 μg/kg, there were no significant differences in consumption between subjects in Groups CL and CW (all P values>.05). The bottom right panel of Fig. 1 presents the mean amount (±S.E.M.) of saccharin consumption for subjects in Groups CL and CW following various doses of L-365,260. Data are presented for eight subjects in each group, except where noted. As illustrated, there were no significant differences in consumption across

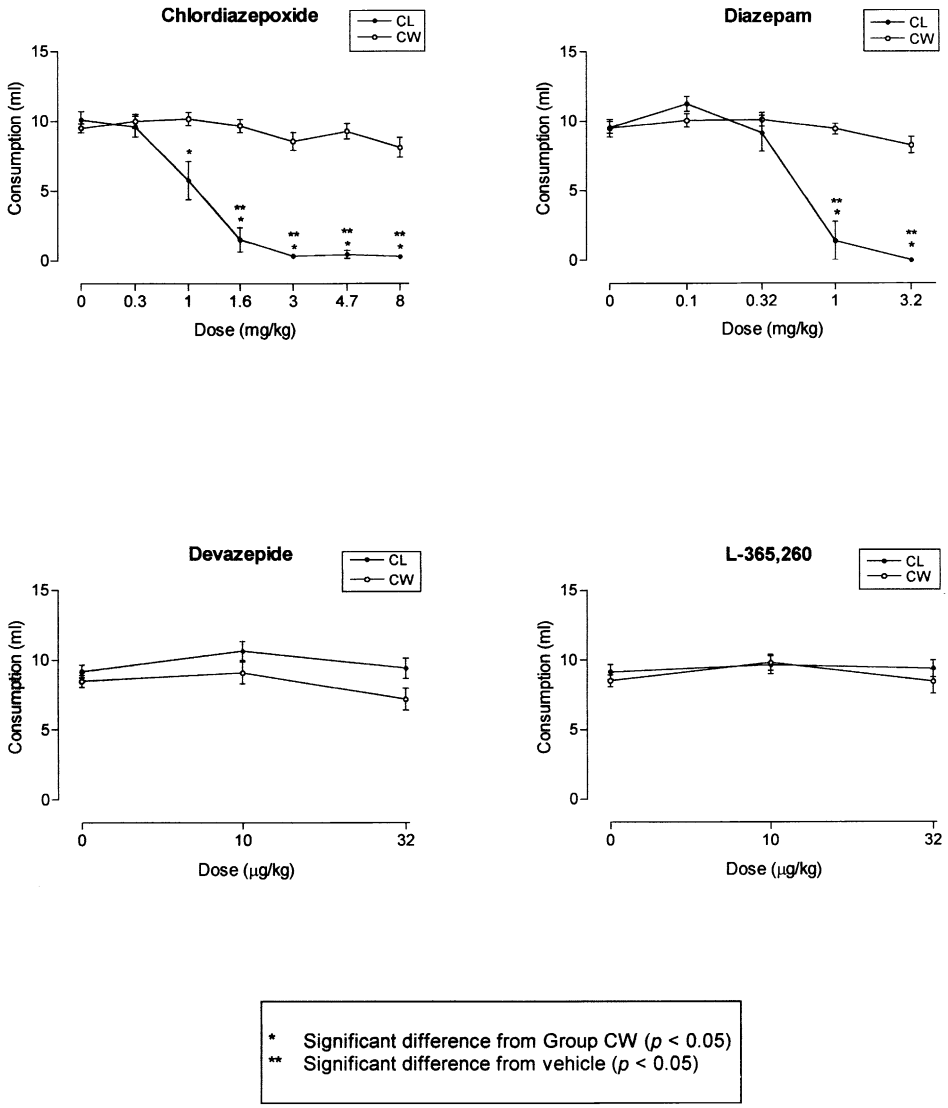

Fig. 1. The mean (±S.E.M.) amount of saccharin consumption of subjects in Groups CL (●) and CW (○) following various doses of CDP (top left panel), diazepam (top right panel), devazepide (bottom left panel) and L-365,260 (bottom right panel).

the doses tested for subjects in either Group CL or CW (all P values > .05). For each dose tested, 0 (for Group CL, $n = 7$), 10 and 32 μg/kg, there were no significant differences in consumption between Groups CL and CW (all P values > .05).

3.3. Phases III and IV: antagonism with CCK and flumazenil

Prior to assessing CCK's ability to antagonize CDP, the potential of CDP to generalize to CCK was assessed (see top panel of Fig. 2). This figure presents the mean amount (±S.E.M.) of saccharin consumed by subjects in Groups CL ($n = 8$) and CW ($n = 9$) following various doses of CCK. As illustrated, there were no significant differences in consumption across the doses tested for subjects in Group CL ($P > .05$). For subjects in Group CW, consumption decreased in a dose-dependent manner (Friedman $\chi^2 = 21$, $P < .001$). There were no significant differences in consumption between subjects in Groups CL and CW at any dose tested (all P values > .05). Fig. 2 also presents the mean amount (±S.E.M.) of saccharin consumed by subjects in Groups CL and CW following the CCK/CDP (bottom left panel) and flumazenil/CDP (bottom right panel) combinations. Data are presented for eight subjects in each group, except where otherwise noted. As illustrated in the bottom left panel, following administration of the CCK and CDP vehicles, subjects in Group CL drank significantly more saccharin than those in Group CN ($U = 8, 40$, $P = .0426$). On the other hand, subjects in Group CL consumed significantly less saccharin than those in Group CW following the CCK vehicle/CDP combination ($U = 0, 48$, $P = .0007$), indicating that the CDP discrimination was maintained during this phase. There was no significant difference in the amount

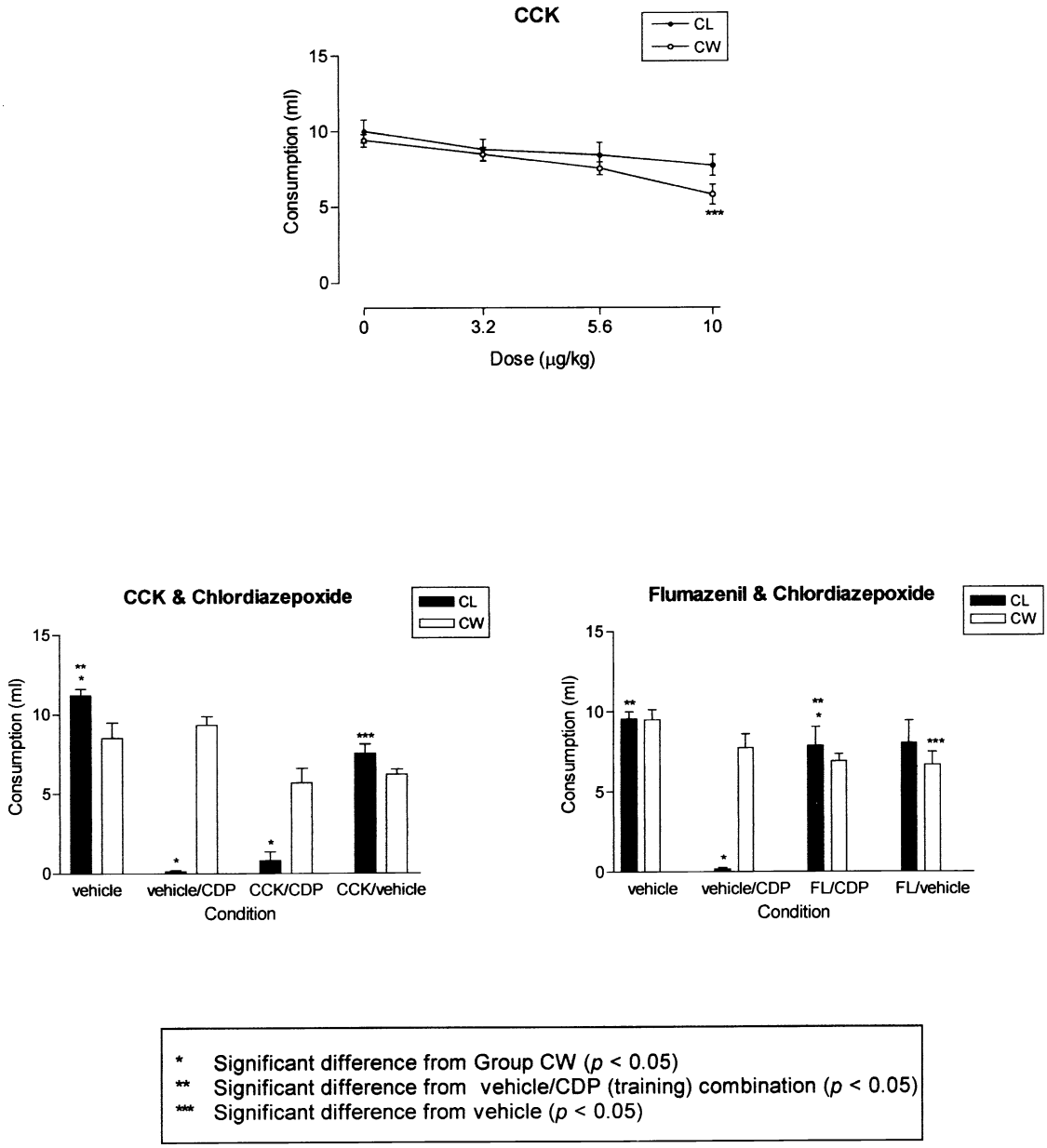

Fig. 2. The mean (±S.E.M.) amount of saccharin consumption of subjects in Groups CL (●) and CW (○) following various doses of CCK (top panel), combinations of 10 μg/kg of CCK or vehicle with an intermediate dose of CDP or vehicle (bottom left panel) and combinations of the training dose of CDP or vehicle with 30 mg/kg of flumazenil (FL) or vehicle (bottom right panel).

consumed by animals in Group CL following the CCK/CDP combination as compared to that following the CCK vehicle/CDP combination ($P > .05$), indicating the inability of CCK to block the discriminative stimulus effects of CDP. Following administration of the CCK/CDP combination, subjects in Group CW drank slightly less (nonsignificant difference; $P > .05$) than that following the CCK vehicle/CDP combination. Further, animals in Group CL consumed significantly less than those in Group CW following administration of the CCK/CDP combination ($U = 2.5, 45.5, P = .0027$). Administration of the CCK/CDP vehicle combination produced a significant decrease in consumption for subjects in Group CL as compared to the CCK and CDP vehicles alone ($W = -36, P = .0078$) and a slight decrease in consumption for subjects in Group CW ($P > .05$). Following the CCK/CDP vehicle combination, there was no difference in consumption between groups ($P > .05$).

As illustrated in the bottom right panel of Fig. 2, following administration of the flumazenil and CDP vehicles alone there were no significant differences in consumption between groups ($P > .05$). On the other hand, subjects in Group CL consumed significantly less saccharin than those in Group CW following the flumazenil vehicle/CDP combination ($U = 0, 48, P = .0007$), indicating

that the CDP discrimination was maintained during this phase. There was no significant difference in consumption for animals in Group CW following administration of the flumazenil/CDP and flumazenil vehicle/CDP combinations ($P > .05$). However, animals in Group CL drank significantly more saccharin following the flumazenil/CDP combination than following the flumazenil vehicle/CDP combination ($W = -28$ $P = .0156$), indicating the ability of flumazenil to block the discriminative stimulus effects of CDP. Following administration of the flumazenil/CDP combination, subjects in Group CL drank significantly more saccharin than those in Group CW ($U = 8.5$, 39.5, $P = .0426$). Administration of the flumazenil/CDP vehicle combination produced no decrease in consumption for subjects in Group CL as compared to the flumazenil and CDP vehicles and a significant decrease in consumption for subjects in Group CW ($W = -21$, $P = .0313$). Following the flumazenil/CDP vehicle combination, there was no difference in consumption between groups ($P > .05$). It should be noted that discriminative control could not be blocked at the training dose of CDP in two animals. For these animals, an attempt was made to block discriminative control at an intermediate dose of CDP (see Methods). For one of these animals, flumazenil blocked discriminative control at this intermediate dose, whereas antagonism was never observed in the other.

4. Discussion

As reported, neither the CCK-A antagonist devazepide nor the CCK-B antagonist L-365,260 substituted for the discriminative stimulus properties of CDP. Further, CCK-8s did not block the stimulus properties of intermediate doses of CDP. The lack of substitution for, or antagonism of, CDP by the CCK antagonists and CCK, respectively, was not due to the inability of this specific design to assess such effects in that the benzodiazepine diazepam did substitute for CDP and the benzodiazepine antagonist flumazenil fully blocked the discriminative effects of CDP.

One possible basis for these findings concerns the assay used in the present experiment to assess the relationship between CCK and GABA. Although the relationship has been reported within a variety of preparations (e.g., Acosta, 1998; Bradwejn and de Montigny, 1984), much of the evidence comes from behavioral models of anxiety (Ballaz et al., 1997; Bickerdike et al., 1994; Biró et al., 1997; Chopin and Briley 1993; Daugé et al., 1989; MacNeil et al., 1997; Matto et al., 1997a; Rex et al., 1994; Singh et al., 1991; Vasar et al., 1994). The present study utilized a drug discrimination procedure, a procedure not necessarily anxiety based. It is possible that a relationship between these compounds necessitates some basal anxiogenic effects that are embedded in the aforementioned models of anxiety. Although possible, it should be noted that the anxiolytic effects of both devazepide (e.g., Matto et al., 1997a,b) and L-365,260 (e.g., Bickerdike et al., 1994; Matto et al., 1997b), as well as the anxiogenic effect of CCK-8s (e.g., Acosta, 1998; Chopin and Briley, 1993), in such models of anxiety are not always reported.

Another possible reason for the failure to find a relationship between CCK and GABA in the present study is that such a relationship could be mediated selectively by CCK-B receptors (see Fink et al., 1998). If so, CCK-4 or another selective CCK-B agonist, rather than CCK-8s, may have blocked the discriminative stimulus effects of CDP. However, mediation by CCK-B receptors cannot entirely explain the relationship between CCK and GABA, as selective CCK-B agonists do not consistently have anxiogenic effects (e.g., Derrien et al., 1994), and CCK-8s, which works primarily at CCK-A receptors, has been shown to be anxiogenic (Biró et al., 1997; Daugé et al., 1989; MacNeil et al., 1997; Vasar et al., 1994). Further, such a position would not explain why the selective CCK-B antagonist L-365,260 failed to block the stimulus properties of CDP in the present study.

The failure of CCK-8s to antagonize the discriminative properties of CDP may be related to the dose of CCK (10 μg/kg) used in the current study. However, this dose of CCK is behaviorally active in a variety of designs (e.g., MacNeil et al., 1997; Melton and Riley 1994; Melton et al., 1993). Further, 10 μg/kg of CCK-8s produced an unconditioned suppression of consumption in both experimental and control animals. Any greater suppression following higher doses of CCK would impede accurate interpretation of the results, in that any antagonism by CCK would be masked by the general suppression of consumption by higher probe doses. In relation to the CCK antagonists, the current study examined the ability of 10 and 32 μg/kg of devazepide and L-365,260 to substitute for CDP. Although such doses of L-365,260 and devazepide have been shown to be behaviorally active in this and other preparations (Ballaz et al., 1997; Harro and Vasar, 1991; Melton and Riley, 1994), it is possible that higher doses of both CCK antagonists may have substituted for CDP. Although possible, several other studies have found an inverted U-shaped dose response curve for both devazepide (e.g., Bickerdike et al., 1994; Chopin and Briley, 1993) and L-365, 260 (e.g., Chopin and Briley, 1993), indicating that higher doses of these CCK antagonists may not have been effective.

In summary, the present results suggest that the CCK antagonists do not share the stimulus properties of CDP and that CCK-8s is not involved in the generation or modulation of its stimulus effects. Thus, within the present design, there is no interaction between CCK and GABA. Such a relationship, however, has been reported within other designs, suggesting that the relationship may be preparation dependent. Many variables may be involved in the relationship between CCK and GABA, and understanding these variables may be important in

providing information into both the etiology of various anxiety disorders, as well as their treatment (e.g., see Bradwejn et al., 1992; Ravard and Dourish, 1990; Shlik et al., 1997).

Acknowledgments

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