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Enhancement of Latent Inhibition in the Rat by the CCK Antagonist Proglumide

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GRACEY, D. J., R. BELL, D. J. KING, K. M. TRIMBLE AND B. J. MCDERMOTT. *Enhancement of latent inhibition in the rat by the CCK antagonist proglumide.* PHARMACOL BIOCHEM BEHAV **59**(4) 1053–1059, 1998.—The behavioral paradigm of latent inhibition (LI) involves the retardation of conditioning to a stimulus when paired with reinforcement, if preexposure to that stimulus with no significant consequence has occurred. This phenomenon is believed to reflect a process of learning to ignore stimuli as irrelevant. Disruption in LI can be considered to be an attentional deficit observed in schizophrenia. The neuropeptide cholecystokinin (CCK), which coexists with dopamine (DA) in some brain regions, has been implicated in the pathophysiology of schizophrenia. The present study examined the effects of the nonselective CCK antagonist proglumide on LI (0.25, 0.5, and 1.0 mg/kg) using a conditioned suppression of drinking procedure in rats. For purposes of comparison the effects of haloperidol (0.1 mg/kg) were also investigated. Administration of 1.0 and 0.5 mg/kg, but not 0.25 mg/kg, proglumide was found to reduce suppression of drinking behavior in animals preexposed (PE) to a flashing light stimulus. These animals developed LI under conditions where preexposed control animals exhibited suppression of drinking behavior similar to that of nonpreexposed (NPE) control animals. These findings for proglumide were comparable to the effects on drinking behavior of 0.1 mg/kg haloperidol. The enhancement of LI by proglumide may be interpreted in terms of CCK–dopamine interactions. Because CCK may modulate dopamine, the results reported here for proglumide strengthen the argument for the investigation of CCK-based drugs as potential antipsychotic agents. © 1998 Elsevier Science Inc.

Proglumide Haloperidol Latent inhibition Rat

NEUROPEPTIDES existing in the central nervous system play a key role in the regulation of normal brain functioning, and have subsequently been studied in cases of functional disturbance (43). Cholecystokinin (CCK) is a peptide widely distributed throughout the brain, where it possess properties of a neurotransmitter (36). Two receptor subtypes have to date been identified—the CCK_A and CCK_B receptors. The distribution of the CCK_B subtype is widespread in the brain. The CCK_A subtype, while present peripherally, has also been found in a number of discrete brain regions (18,28,27). The presence of high levels of CCK in the mesocorticolimbic pathway and limbic lobe, sites relevant to schizophrenia, suggests a possible role for CCK in the pathophysiology and treatment of this disorder (33).

Pharmacological manipulation of the CCK system as an approach to treating schizophrenia was initially raised with the observed colocalization of CCK with dopamine (DA) in the mesolimbic pathway (19). A principle antipsychotic action of antipsychotic drugs may be the blockade of DA receptors in this system (24). Chronic antipsychotic treatment also alters mesolimbic CCK function (34). CCK demonstrates an ability to mimic the action of antipsychotics to inhibit DA firing in the mesolimbic system. This suggests the status of CCK as an endogenous antipsychotic substance (42).

Most of the evidence supporting a role for the CCK-based therapy in the treatment of schizophrenia is based on animal models demonstrating an antipsychotic-like profile (7). These models, such as catalepsy and conditioned avoidance responding, which are primarily a function of dopaminergic blockade, have produced rather contradictory findings. CCK has been shown to both inhibit and facilitate DA-mediated behaviors in the mesolimbic pathway (8,23,41). Such effects are readily apparent in the nucleus accumbens (NAC). This region is one of the major terminal fields of CCK–DA coexist-

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ence, receiving dense projections from the ventral tegmental area (19). Studies have shown that CCK, when administered with DA into the rat posterior NAC, potentiated DA-induced hyperlocomotion (9). CCK administered into the anterior NAC had no effect, or inhibited DA-induced hyperlocomotion (9). Facilitation of DA-induced hyperlocomotion demonstrated a CCK_A receptor pharmacology, and inhibitory effects of a CCK_B receptor pharmacology. It seems probable that CCK interacts with DA in a different way in regions where CCK–DA coexistence occurs, such as the posterior NAC, compared to brain regions, including the anterior NAC, which receive CCK from nondopaminergic fibers (9).

Early clinical studies that examined the effects of CCK administration in treating schizophrenia were largely disappointing. Initially promising investigations were negated by later controlled, double-blind studies that showed no significant effects on schizophrenic patients (25). CCK's failure to improve schizophrenic symptoms has prompted a reexamination of the pharmacological properties of CCK-based drugs. To demonstrate any clinical efficacy it is important that these compounds are stable, have a long half-life in vivo, are resistant to metabolic degradation, and are able to cross the blood–brain barrier (43). Recent years have seen clear advances, both in understanding the nature of CCK-DA interactions, and in the development of better CCK-based drugs. Indeed, after many years of speculation regarding CCK as an endogenous antipsychotic substance (42,57), some studies have suggested that CCK antagonists would be a more suitable basis for antipsychotic treatment (31,32). Animal models that are relevant to schizophrenia now have a role to play in identifying the best CCK drugs to test for antipsychotic activity.

Most of the evidence supporting a role for the CCK-based therapy in schizophrenia is based on animal screens demonstrating an antipsychotic-like profile (5,35). In terms of validity, these models, such as catelepsy and conditoned avoidance responding, possess solely predictive validity and are primarily a function of dopaminergic blockade, which rather limits their ability to detect novel antipsychotic agents (34). Attempts to model specific aspects of the disease state have produced models of schizophrenia with much stronger overall validity. The latent inhibition (LI) model is one of a number of models said to possess construct validity (14). The LI phenomenon occurs when preexposure to a stimulus that is devoid of any consequence retards subsequent learning involving that stimulus. This retardation has been considered mostly in terms of engagement of attention and the formation of new associations (22). LI has emerged as an animal model of schizophrenia on the proposed basis that disruption in such a learning process, i.e., an inability to ignore irrelevant stimuli, may be a prominent characteristic element of the disease state.

The LI effect, and its response to drug treatment, has been demonstrated behaviorally in both animals and humans. LI is disrupted in the rat by amphetamine administration (11,21,37, 38,40,45,46,48) and enhanced by antipsychotic administration (4,13,15,21,26,29,37,40,47,51,52,53). A number of human studies have reported a disruption of LI in acute schizophrenics (1,17), and in nonschizophrenic volunteers following treatment with amphetamine (16), as well as an enhancing effect with the antipsychotic, haloperidol, in healthy people (56).

Within the LI paradigm Weiner et al. (49,50) have further investigated the potential antipsychotic action of CCK. They employed the angiotensin-converting enzyme (ACE) inhibitor ceronapril in the supposition that, because ACE is one of the peptidases by which CCK is degraded, an ACE inhibitor might raise CCK levels in the brain. They reported, however, that ceronapril had opposite effects on LI dependent on acute (an enhancing effect) vs. chronic (a disruptive effect) administration.

Although the modulatory effects that CCK reportedly exerts on dopaminergic activity are quite complex, there are some studies that suggest that CCK can actually enhance DA function (31,32). This, coupled with the largely negative findings that have emerged from clinical studies on the use of CCK analogues in the treatment of schizophrenia, has focused attention on an alternative possibility—that CCK antagonists may possess antipsychotic potential. The present study investigated the effects of the CCK antagonist, proglumide (0.25, 0.5, and 1.0 mg/kg), administration on LI in the rat using a three-stage conditioned emotional response procedure as developed by Feldon and Weiner (15) and Weiner (54). In stage one, a to-be-conditioned stimulus, flashing houselight, was preexposed without consequence. In conditioning, stage two, the flashing houselight stimulus was paired with a mild foot shock. In the final test stage LI was indexed by the degree of suppression of water licking elicited by a flashing houselight stimulus. The use of ten preexposures in this study allows for an improved evaluation of facilitatory drug effects, given that untreated preexposed animals would not be expected to elicit LI (13,27,54). An enhancing effect has been established for the D_2 antagonist, haloperidol (4,13,15,29,48,53). To avoid false negative conclusions, this study included both a positive (0.1 mg/kg haloperidol) and a negative (vehicle) control.

METHOD

Subjects

Male, Sprague–Dawley rats (Laboratory Services, Medical Biology Centre, Queen's University Belfast), weighing 260–425 g, were housed two to a cage on a reverse 12 D:12 L (lights off at 0700 h). One week after house pairing (day 8 of the experiment), animals were placed on a water deprivation (23 h) schedule that continued throughout the experiment. Experimental manipulations were conducted during the dark phase of the light/dark cycle.

Apparatus

Experiments took place in three locally constructed metal Skinner boxes (24.5 × 24.5 × 21 cm measured from a raised grid floor) enclosed in a ventilated, sound- and light-attenuating Campden Instrument Chest. A tray containing sawdust was located under each Skinner box. Licks from a removeable drinking bottle (positioned on the chamber wall 2.0 cm above the grid floor and accessible through a hole 1.0 cm in diameter) were registered by a drinkometer circuit (Campden Instruments, Model 453). The preexposure and conditioned stimulus was a flashing light set in the roof of the chamber. The test chamber floor was a shock grid formed by steel bars (0.5 cm in diameter) spaced 1.0 cm apart. The shock source came from a Campden Instruments shock generator (Model 521/C) and shock scrambler (Model 521/S), with a setting of 0.5 mA shocks running through the grid bars. BBC Microcomputers, with a SPIDER extension for on-line control (Paul Fray Ltd., Cambridge, UK), were used for equipment programming and data recording.

Procedure

Following house pairings, animals were randomly assigned to the various treatment conditions. They were also allocated

to one of the three Skinner boxes, which was to be the only box experienced during the course of the experiment. On days 8 to 16 rats were handled for approximately 3 min per day to minimize stress during the experiment.

Baseline (days 15–19). One week after water deprivation began, animals under went a period of pretraining. Animals were individually placed in their assigned Skinner boxes and allowed to drink for 15 min each day for 5 consecutive days. After being returned to their home cage, animals received access to water for a further 45-min period.

Preexposure (day 20). In accordance with their assigned treatment conditions, animals in the unlit test cage received a predetermined number (0 for NPE rats and 10 for PE rats) of preexposures to the flashing houselight (10-s duration, three flashes per second), with a fixed interstimulus time of 50 s. When the 10-min preexposure period had ended animals were returned to their home cages. Access to water in the home cage was set at 1 h, given that an off-baseline procedure (no water access during preexposure or conditioning) was used.

Conditioning (day 21). All subjects were given two light-shock pairings spaced over 15 min. The first pairing was delivered after 5 min (houselight parameters matched those of the preexposure period, followed immediately by a 0.5-mA, 1-s foot shock). The second light-shock pairing was given 5 min later. An additional 5-min period elapsed before the rat was returned to its home cage and allowed access to water for 1 h.

Rebaseline (day 22). Identical to the baseline sessions, animals were allowed to drink for 15 min. Rats were then returned to their home cages and given access to water for 45 min.

Test (day 23). Animals in their assigned Skinner box were given access to the drinking bottle. Upon completion of 75 licks the flashing houselight stimulus was presented until 5 min had elapsed from stimulus onset. The log times between licks 1–75, 51–75 (time A) and 75–100 (time B) were recorded. LI was assessed via two measures. The first method was simply to take the time for an animal to make licks 75–100 (time B). The second method involved calculating a suppression ratio, the formula being time A/time A + time B. A suppression ratio close to 0.01 indicates a complete suppression of drinking behavior (no LI), while a suppression ratio of 0.50 indicates no change in response rate from the prestimulus period to the stimulus-on period (LI).

Those animals that did not begin to lick within 10 min were not presented with the flashing houselight stimulus, but were removed and retested within 2 h. Animals that failed to drink on retest were discarded from the experiment. If an animal failed to reach 100 licks within 300 s, a value of 300 was assigned to its time B.

Drug Treatment

Three doses of proglumide (0.25, 0.5, and 1.0 mg/kg) and one dose of haloperidol (0.1 mg/kg) were tested. Proglumide solutions were prepared by dissolution in water. Haloperidol was dissolved in dilute acetic acid (100 ml glacial acetic acid in 20 ml double distilled water) and neutralized in 105 ml of 5 M NaOH. The solution was then diluted to the appropriate concentrations using double distilled water.

All injections, including vehicle injections, were given as 1 ml/kg intraperitoneally (IP) 45 min before preexposure and before conditioning. Both rebaseline and test were conducted drug free. Drugs were obtained from Research Biochemicals Inc. (Natick, MA).

Ninety-three animals were divided randomly into 12 experimental groups in a 2×6 factorial design. Data from three rats was lost due to apparatus failure (one NPE rat treated with 0.1 mg/kg haloperidol, one NPE rat treated with 1.0 mg/kg proglumide, and one PE rat treated with 0.25 mg/kg proglumide). Two animals failed to drink on retest (one NPE animal treated with 1.0 mg/kg proglumide and one PE animal treated with 0.5 mg/kg proglumide) and were discarded from the experiment. Final analysis was conducted on a data set derived from 88 subjects.

Statistical Analysis

Mean log times to complete licks 1–75, licks 75–100, and suppression ratios were analyzed using a 2×6 ANOVA with main factors of preexposure (PE and NPE) and drug (1.0, 0.5, and 0.25 mg/kg proglumide and appropriate vehicle, 0.1 mg/kg haloperidol and appropriate vehicle). A $2 \times 6 \times 10$ ANOVA was carried out on the bins measure with main factors of preexposure (PE and NPE), drug (1.0, 0.5 and 0.25 mg/kg proglumide and appropriate vehicle, 0.1 mg/kg haloperidol and appropriate vehicle) and bins [1–10].

Statistical comparisons to establish the presence or absence of LI for individual treatments used the post hoc parametric Newman–Keuls test. Considered in terms of the values for suppression ratios or log times to make licks 75–100, the presence of a statistically significant difference between PE and NPE groups receiving the same treatment indicated that an LI effect had occurred.

RESULTS

Log Time to Make Licks 1–75

No significant differences between any of the 12 experimental groups were found in terms of their (log) times to complete licks in the period prior to stimulus onset. A 2×6 ANOVA with main factors of preexposure (PE and NPE) and drug (1.0, 0.5, and 0.25 mg/kg proglumide and appropriate vehicle, 0.1 mg/kg haloperidol and appropriate vehicle) produced no significant outcomes for either of the two main effects, or for their interaction.

Suppression Ratios

Figure 1 presents the mean suppression ratios for both PE and NPE animals in the six drug conditions. In both the proglumide and haloperidol control groups there was a high degree of suppression of drinking behavior. Comparatively, at 1.0 mg/kg and 0.5 mg/kg proglumide, as well as 0.1 mg/kg haloperidol, PE animals exhibited less suppression of drinking than the same dosage NPE animals. This constitutes an LI effect at these doses, under conditions where LI would not occur in normal animals. An LI effect was not, however, apparent with the lowest dose of proglumide tested. Both PE and NPE (0.25 mg/kg proglumide) groups exhibited a similar suppression of drinking behavior. A 2×6 ANOVA performed on suppression ratios, with main factors of preexposure (PE and NPE) and drug (1.0, 0.5, and 0.25 mg/kg proglumide and appropriate vehicle, 0.1 mg/kg haloperidol, and appropriate vehicle), yielded significant main effects of preexposure, $F(1, 76) = 30.642$, $p < 0.0001$, and drug, $F(5, 76) = 9.264$, $p < 0.0001$, with a significant preexposure $\times$ drug interaction, $F(5, 76) = 5.747$, $p < 0.001$.

The Newman–Keuls test revealed highly significant differences ($p < 0.01$) between the PE (1.0 mg/kg proglumide) group and all other experimental groups, with the exception of the PE (0.5 mg/kg proglumide) group ($p < 0.05$) and the PE (0.1 mg/kg haloperidol) group (nonsignificant difference).

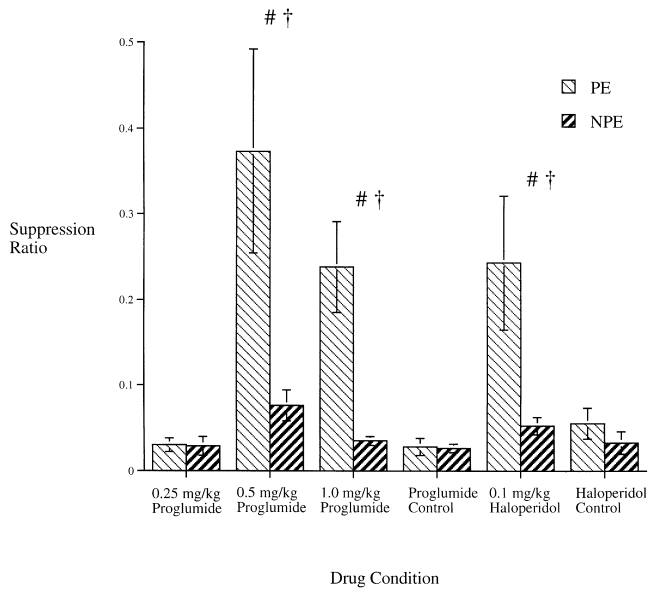

FIG. 1. Mean suppression ratios of the preexposed (PE) and nonpreexposed (NPE) under six drug conditions: 0.25 mg/kg proglumide, 0.5 mg/kg proglumide, 1.0 mg/kg proglumide control, 0.1 mg/kg haloperidol, and haloperidol vehicle. 0.5 = no suppression of drinking behavior (LI), 0.01 = complete suppression (no LI). Signifiacnt values refer to comparisons with vehicle control (#, $p < 0.01$) and nonpreexposed counterparts (†, $p < 0.01$).

Highly significant differences ($p < 0.01$) were also found between the PE (0.5 mg/kg proglumide) group and all other experimental groups, with the exception of the PE (1.0 mg/kg proglumide) group ($p < 0.05$) and the PE (0.1 mg/kg haloperidol) group ($p < 0.05$).

Newman–Keuls analysis further detailed significant differences ($p < 0.01$) between the PE (0.1 mg/kg haloperidol) group and all other experimental groups, with the exception of the PE (0.5 mg/kg proglumide) group ($p < 0.05$) and the PE (1.0 mg/kg proglumide) group (nonsignificant difference).

Log Times to Make Licks 75–100

Figure 2 shows the mean log times to complete licks 75–100 in the presence of a flashing houselight stimulus for both PE and NPE animals in the six drug conditions. The high degree of suppression of drinking is apparent in the significantly greater times taken to make a further 25 licks upon stimulus onset for the PE and NPE (proglumide vehicle), PE and NPE (haloperidol vehicle), and the PE and NPE (0.25 mg/kg proglumide) groups. Comparatively, PE animals in the 1.0 mg/kg and 0.5 mg/kg proglumide conditions, as well as the 0.1 mg/kg haloperidol control, took significantly less time to make these additional 25 licks in the presence of a flashing houselight stimulus, which indicates a lower suppression of drinking behavior and the presence of an LI effect. A 2 × 6 ANOVA was performed on mean log lick times for licks 75–100 with main factors of preexposure (PE and NPE) and drug condition (1.0, 0.5, and 0.25 mg/kg proglumide, proglumide vehicle, 0.1 mg/kg haloperidol, and haloperidol vehicle). Significant effects of preexposure, $F(1, 76) = 24.959$, $p < 0.0001$, and drug, $F(5, 76) = 12.649$, $p < 0.0001$, were revealed. The interaction between preexposure and drug was also found to be significant, $F(5, 76) = 4.041$, $p < 0.01$.

A Newman–Keuls was performed on the preexposure × drug interaction. Findings were consistent with analysis for suppression ratios, with the exception that differences between the PE (1.0 mg/kg proglumide) and PE (0.5 mg/kg proglumide) groups, and the PE (0.1 mg/kg haloperidol) and PE (0.5 mg/kg proglumide) groups were not significant.

DISCUSSION

The present experiment's use of a low number of stimulus preexposures ($n = 10$) meant that an LI effect was not detectable in both vehicle groups regardless of whether or not the animals had been preexposed to the flashing light stimulus. An LI effect was, however, detectable in animals receiving either 1.0 mg/kg proglumide, 0.5 mg/kg proglumide, or 0.1 mg/kg haloperidol. The enhancement of LI in these treatment groups stems from the fact that PE animals showed less suppression of drinking in the presence of a flashing houselight, compared with NPE animals.

The facilitatory effect on LI reported for haloperidol is consistent with previous findings (4,13,15,29,40,47,53). The enhancement of LI by proglumide is comparable to haloperidol's effect. In particular, drug effects for both compounds were only demonstrable in PE animals.

An enhancement of LI was achieved with the two higher doses of proglumide (0.5 and 1.0 mg/kg). However, PE animals receiving the lower proglumide dose (0.25 mg/kg) did not demonstrate LI. This suggests a rather limited effective dose range for proglumide.

It is possible to interpret these findings for proglumide in terms of CCK–DA interactions. Although a number of authors have suggested that CCK may act to reduce central dopaminergic function and therefore possess antipsychotic-like properties (42,58), this fails to incorporate the excitatory effect CCK is known to exert on dopaminergic functioning

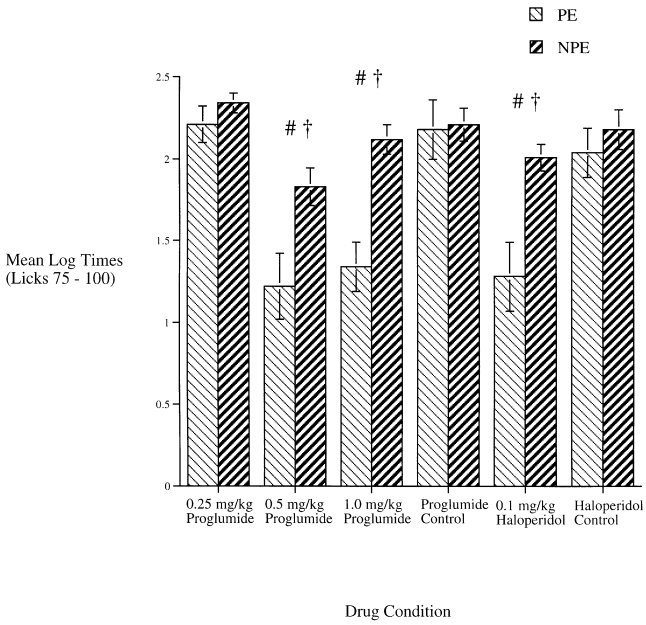

FIG. 2. Mean log times for 75–100 licks of the preexposed (PE) and nonpreexposed (NPE) groups under six drug conditions: 0.25 mg/kg proglumide, 0.5 mg/kg proglumide, 1.0 mg/kg proglumide control, 0.1 mg/kg haloperidol, and haloperidol vehicle. Significant values refer to comparisons with vehicle control (#, $p < 0.01$) and nonpreexposed counterparts (†, $p < 0.01$).

(31,32). This excitatory effect in regions relevant to schizophrenia, such as the NAC and ventral tegmental area, suggests the use of a CCK antagonist in antipsychotic treatment (31,32). Proglumide's enhancement of LI, as reported in this study, would certainly support such a position. However, given that this compound does not show any selectivity for either of the two CCK subtypes, it is not clear which one of the CCK receptors (CCK_A or CCK_B) is primarily involved in proglumide's facilitatory effect. Further studies, using more recently developed subtype-selective CCK antagonists, are being performed in the authors' laboratory.

Proglumide has been shown to selectively antagonize CCK-induced excitation of midbrain DA neurons (3). Further, in behavioral studies low doses of proglumide (0.2 mg/kg) enhance the effect of haloperidol on certain mesolimbic, but not nigrostriatal, DA functions (10). This may be important because the therapeutic action of antipsychotic drugs has been related to action on mesolimbic DA receptors, while their effects on nigrostriatal DA receptors have been implicated in the inducement of EPS. There is also evidence to suggest that the establishment of LI is mediated by the mesolimbic DA system (11,50). Furthermore, CCK colocalization with DA has been shown to be more prevelant in the mesolimbic than the nigrostriatal DA pathway (19).

Not all studies have, however, been consistent with the notion that proglumide may be a useful adjunct therapy to standard antipsychotic treatment. In the only controlled clinical study to date, Whiteford et al. (55) reported no significant effects with proglumide on patients already on antipsychotic (haloperidol) treatment. However, given that in preclinical studies proglumide caused a left shift in potency without changing overall efficacy in animals treated with haloperidol (10), it may not have been possible to enhance the clinical effects of the high doses of haloperidol that patients were receiving. Clinical studies into the effects of administering CCK antagonists alone will have to wait until the antipsychotic potential of CCK-based drugs has been more firmly established.

Although proglumide may be viewed as having an antipsychotic profile, both from this and earlier behavioral studies, a role for CCK in anxiety has also been raised. In particular, CCK_B antagonists have been shown to possess anxiolytic properties in both animal models of anxiety (20) and in clinical trials (2). However, given that proglumide did not reduce conditioned suppression in any of the NPE groups, there is no evidence, at least within the dose range used, to indicate that proglumide was exerting an anxiolytic effect in this study. Further, even though the conditioned emotional response can be used as an animal model of anxiety (39), no drug was administered on the actual day of testing using this procedure.

Apart from its modulating effects on DA, CCK also interacts with several other neuronal systems, including the GABAergic (12) and serotonergic (30) systems. Therefore, the possibility that proglumide, in enhancing LI, may be influencing nondopaminergic systems cannot be excluded. Although the involvement of the GABAergic system in LI has yet to be directly studied, a number of investigations have indicated that the serotonergic system may play a role in LI's development. In particular, this neuronal system is believed to interact with the CCK-ergic system via the $5\text{-}HT_3$ receptor (30). Moran and Moser (27) and Warburton et al. (44) have both reported an enhancement of LI with $5\text{-}HT_3$ antagonists.

Proglumide's reported enhancement of LI may best be considered in terms of CCK–DA interactions. First, CCK has a proposed excitatory effect on dopaminergic functioning (31,32). Second, the antagonism of CCK-induced excitation by proglumide has been identified as occurring in a region specifically implicated in LI—the mesolimbic DA system (10). In particular, proglumide may be acting to antagonize CCK's excitatory effects on DA in the posterior NAC (9). Excitatory effects of CCK have, however, been reported in other brain regions implicated in LI, such as the hippocampus (54). It cannot be ruled out that proglumide is also having an effect in these regions. Given that the effects of CCK on dopaminergic function depends, in part, on the anatomical site of administration (6), it would be useful to specify, via microinjection studies, precisely which brain regions are involved in the enhancement, and indeed possibly the disruption, of LI.

In conclusion, the present study demonstrates an enhancement of LI, under reduced stimulus preexposure conditions, by the CCK antagonist proglumide (1.0 and 0.5 mg/kg). Given that its behavioral profile in LI is similar to that of haloperidol shown in this study, as well as a range of typical and atypical antipsychotic agents that have been previously tested (13,15, 21,26,27,50,52), this effect may be predictive of proglumide's antipsychotic activity. Such findings for proglumide strengthen the argument for further investigations of CCK-based drugs within an animal model found to be both relevant to the clinical syndrome, and which demonstrates an ability to detect antipsychotic potential in compounds with differing modes of action.

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