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PD-135,158, a Cholecystokinin$_B$ Antagonist, Enhances Latent Inhibition in the Rat

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GRACEY, D. J., R. BELL AND D. J. KING. *PD-135,158, a cholecystokinin$_B$ antagonist, facilitates latent inhibition in the rat.* PHARMACOL BIOCHEM BEHAV **65**(3) 459–463, 2000.—The antipsychotic potential of cholecystokinin (CCK)-related compounds stems from CCK's colocalization with dopamine (DA). CCK demonstrates excitatory and inhibitory effects on DA in the mesolimbic pathway. Such diverse actions might be mediated by different receptor subtypes (CCK_A or CCK_B). Multiple hypotheses have emerged regarding the clinical application of CCK-based drugs. Administering selective nonpeptide antagonists within animal models relevant to schizophrenia would help delineate CCK receptor involvement. One animal model simulating a cognitive dysfunction of schizophrenia is latent inhibition (LI). An animal repeatedly exposed to a stimulus that is devoid of consequence is subsequently inhibited in making new associations with that stimulus. This reflects a process of learning to ignore irrelevant stimuli. The present study examined the effects of the selective CCK_B antagonist PD-135,158 (0.001, 0. 01, and 0.1 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. PD-135,158 (0.1 mg/kg), similar to haloperidol (0.1 mg/kg), elicited a clear LI effect under conditions that did not lead to LI in control rats (low number of preexposures). These findings highlight the antipsychotic potential of CCK_B antagonists, and further illustrate the LI paradigm's capacity to detect novel, antipsychotic-like, drug activity. © 2000 Elsevier Science Inc.

PD-135,158 CCK Latent inhibition Rat model of psychosis

THE neuropeptide cholecystokinin (CCK) is present throughout the central nervous system and, in its capacity as a neurotransmitter (29), has been implicated in both normal and abnormal brain functioning (38). What role CCK might play in the pathophysiology of schizophrenia has been the subject of a considerable body of preclinical research. Behavioral studies, using simple rodent paradigms, have revealed the antipsychotic-like properties of CCK. This neuropeptide produces catalepsy (5), decreases locomotion (2), and inhibits amphetamine-induced rearing behavior (28).

Although CCK s interaction with other neurotransmitter systems has been well documented [see (37)], what is of particular importance with respect to schizophrenia is the finding that CCK is extensively colocalized with dopamine (DA) in the mesolimbic pathway (16). In its ability to inhibit DA firing in the mesolimbic system, CCK mimics a principal antipsychotic drug action (18). Conversely, antipsychotic drug treatment is known to alter mesolimbic CCK function (27). This suggests that part of the role of CCK in the central nervous system might be to act as an endogenous antipsychotic substance. Accordingly, the use of CCK agonists has been proposed as a novel treatment strategy for schizophrenia (39).

Early clinical trials of CCK agonists did not produce the beneficial effects on schizophrenic symptomatology indicated by numerous preclinical findings. Initially, promising investigations were later negated by controlled, double-blind studies that showed no significant effects on schizophrenic patients (20). In light of these negative findings, a reexamination of precisely what role CCK plays in regulating DA activity has inevitably followed. This has been greatly aided by the recent development of an improved class of CCK based drugs. Nonpeptide CCK ligands are notable for their stability, long half-life in vivo, resistance to metabolic degradation, and ability to cross the blood–brain barrier (38). Through the use of such compounds, hypotheses have emerged that run contrary to the earlier notion that CCK agonists possess antipsychotic potential. Thus, an alternative rationale, for the use of CCK antagonists in the treatment of schizophrenia, is based on the premise that CCK exerts an excitatory effect on dopaminergic activity in regions relevant to schizophrenia,

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such as the nucleus accumbens (NAC) and ventral tegmental area (VTA) (24,25).

Those animal models that were initially used to evaluate, and that subsequently supported, CCK-based therapy in schizophrenia treatment have also been reexamined. Models such as catalepsy and conditioned avoidance response, while being established as DA-dependant paradigms, do not bear any obvious relation to the symptoms of the disease state. Their limited, predictive validity means that such models are unlikely to identify novel antipsychotic agents (27). Indeed, later studies using these types of models have failed to clearly demonstrate an antipsychotic like profile for CCK antagonists (6). The need exists, therefore, to test recently developed nonpeptide CCK ligands in a more suitable animal model for schizophrenia. 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 said to possess construct validity (9). The LI effect occurs when an animal that has been repeatedly exposed to a stimulus without consequence later becomes inhibited in making any new associations with that stimulus. Insofar as this reflects an ability to ignore irrelevant stimuli, LI has come to serve as an animal model for attentional deficit in schizophrenia.

The LI phenomenon, and its responsivity to drug treatment, is apparent in both animals and humans. LI is disrupted in the rat following amphetamine treatment (30,42,43). Consistent with these preclinical findings, LI is also reportedly disrupted in acute schizophrenics (1,14,32) and in nonschizophrenic volunteers receiving amphetamine (13,33). Preclinical studies have also shown how LI can be potentiated in animals following treatment with a range of pharmacologically distinct typical and atypical antipsychotics (4,8,11,34,35,46), a rather unique behavioral effect given that it was not initially induced by a DA agonist. Furthermore, potentiation of LI has also been reported in healthy people following treatment with the antipsychotic haloperidol, although this only occurred using a visual task procedure (47,48).

Weiner et al. (44,45) have used the LI paradigm to examine the behavioral consequences of altering CCK levels in the rat brain. Consistent with earlier theories about the antipsychotic potential of CCK agonists (39), they proposed that by inhibiting angiotensin converting enzyme (ACE), one of the peptidases involved in the degradation of CCK, central CCK levels might be raised. Findings with the ACE inhibitor ceronapril were, however, equivocal—producing a biphasic effect dependant on acute (enhancement) or chronic (disruption) treatment. Recently, we have demonstrated that the CCK antagonist proglumide enhances LI (12). There are, however, two CCK subtypes that have been identified—CCK_A and CCK_B—which may be differentiated according to their affinity for CCK fragments and analogs (6). These two can also be differentiated behaviorally. For example, in the NAC facilitation of DA- and amphetamine-induced hyperlocomotion demonstrate a CCK_A receptor pharmacology, and inhibitory effects a CCK_B receptor pharmacology (7,36). Given, then, that proglumide is a nonsubtype selective CCK antagonist, it remains to be ascertained which (CCK_A or CCK_B) is primarily implicated in this compound's facilitatory effect on LI. Our rationale for examining the behavioral effects of a CCK_B antagonist is based on a series of electrophysiological studies showing that CCK_B antagonists reduce midbrain DA neuronal activity (22,23,25). In view of this, the present study examined whether the CCK_B antagonist PD-135,158 (0.001, 0.01, and 0.1 mg/kg) would potentiate LI.

PD-135,158 is an extremely potent displacer of binding from CCK_B receptors, with an IC_{50} value in the low nanmolar range (IC_{50} = 3.5 nM) (17). A three-phase conditioned emotional response (CER) procedure was used (40,41), with animals being preexposed to a low number of stimulus presentations. This would allow for a more suitable evaluation of any facilitatory drug effects, given that untreated preexposed animals would not be expected to show LI (40). The D_2 antagonist haloperidol (0.1 mg/kg), which has consistently exhibited an enhancing effect on LI in our hands (12,34,35), served as a positive control.

METHODS

Subjects

Male, Sprague–Dawley rats (Laboratory Services, Medical Biology Centre, Queen's University Belfast), weighing 243–440 g, were housed two to a cage under reversed cycle lighting. One week after house pairing (day 8 of the experiment), animals were placed on a water deprivation (23 h) schedule. During days when water was available in the Skinner boxes this time was subtracted from the 1-h daily ration given in the home cages. On days 8 to 14 rats were handled for approximately 3 min per day to minimize stress during the experiment.

Apparatus

Experiments took place in six locally constructed metal Skinner boxes enclosed in a Campden Instrument Chest. Licks from a removeable drinking bottle 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. 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. All equipment control and data collation was governed by a single RISC PC computer, with an ARACHNID extension for online control (Paul Fray Ltd., Cambridge, UK).

Procedure

Baseline (days 15–19). Animals were placed in their assigned Skinner boxes and allowed to drink for 15 min each day for 5 consecutive days.

Preexposure (day 20). With the water bottle removed animals received a predetermined number (0 for nonpreexposed (NPE) rats and 10 for preexposed (PE) rats) of preexposures to the flashing houselight (10-s duration, three flashes per s), with a fixed interstimulus time of 50 s.

Conditioning (day 21). With the water bottle removed, all subjects were given two light-shock pairings spaced over 15 min and presented 5 min apart. Houselight parameters matched those of the preexposure period, followed immediately by a 0.5-mA, 1-s footshock.

Rebaseline (day 22). Animals received a drinking session identical to baseline sessions.

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 times between licks 1–75, 51–75 (time A: prestimulus time) and 75–100 (time B: on-stimulus time) were recorded. LI was assessed using a suppression ratio calulation, the formula being time A/time A + time B. Suppression ratio data were then subject to log transformations. If a log suppression ratio value tends towards

zero, this indicates that an animal is increasingly less suppressed in its drinking behavior.

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 PD-135,158 (0.001, 0.01, and 0.1 mg/kg) were tested. Solutions were prepared by dissolution in water. Injections were given in 0.2 ml/kg SC 30 min before prexposure and conditioning.

Haloperidol (0.1 mg/kg) 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. Injections were given in 1.0 ml/kg 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).

Eighty animals were divided randomly into 12 experimental groups in a 2 × 6 factorial design. Animals were divided into experimental groups in the following manner: 0.001 mg/kg PD-135,158 PE = 7, NPE = 7; 0.01 mg/kg PD-135,158 PE = 6, NPE = 7; 0.1 mg/kg PD-135,158 PE = 6, NPE = 6; PD-135,158 control PE = 6, NPE = 7; 0.1 mg/kg haloperidol PE = 8, NPE = 8; haloperidol vehicle PE = 5, NPE = 7. Data from two rats were lost due to apparatus failure (one PE animal treated with 0.1 mg/kg haloperidol and one NPE animal treated with haloperidol vehicle). Three animals failed to drink at retest (one PE animal treated with 0.01 mg/kg PD-135,158, one PE animal treated with 0.1 mg/kg PD-135,158 and one NPE animal treated with 0.1 PD-135,158). These animals were discarded from the experiment. Final analysis was, therefore, conducted on a data set derived from 75 subjects.

Statistical Analysis

Log times to complete licks 1–75 and log suppression ratios of the 12 groups were compared using one-way ANOVA. Methods of contrasts was used to test the 6 a priori hypotheses. An adjustment for multiple comparisons was then made using Bonferroni corrections.

Considered in terms of the values for log suppression ratios, the presence of a statistically significant difference between PE and NPE groups receiving the same treatment indicated that an LI effect had occurred.

The experimental protocol was in compliance with the UK Animals Scientific Procedures Act 1986.

RESULTS

Log Time to Make Licks

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 (see Table 1).

Log Suppression Ratios

Figure 1 presents the mean suppression ratios for both PE and NPE animals in the 12 experimental conditions. Results indicate significant differences between the groups, $F(11, 74) = 4.289$, $p < 0.001$. Post hoc Bonferroni revealed significant differences between PE and NPE animals at the highest dose of PD-135,158 (0.1 mg/kg) tested, as well as at the 0.1 mg/kg haloperidol dose. Furthermore, the trends support a dose-dependent effect for PD-135,158.

TABLE 1

TABLE OF MEAN LOG TRANSFORMED A PERIODS (IN SECONDS)

Drug	Preexposed	Nonpreexposed
PD-135, 158		
0.001 mg/kg	1.26 ± 0.09	1.13 ± 0.09
0.01 mg/kg	1.29 ± 0.10	1.58 ± 0.17
0.1 mg/kg	1.20 ± 0.10	1.40 ± 0.23
Vehicle	1.19 ± 0.13	1.46 ± 0.20
Haloperidol		
0.1 mg/kg	1.29 ± 0.13	1.10 ± 0.03
Vehicle	1.32 ± 0.20	1.19 ± 0.11

Time A period is the time taken to complete licks 1–75, prior to stimulus onset.

DISCUSSION

In the present study, and with the use of a low number of prexposures, treatment with 0.1 mg/kg haloperidol produced, as expected, a significant LI effect. A facilitation effect on LI was also demonstrated for the CCK_B antagonist PD-135,158 (0.1 mg/kg). Importantly, both drugs appear to be having an effect solely on PE animals. Although a weak LI effect was apparent in the PD-135,158 vehicle condition, this proved to be nonsignificant. Furthermore, PE animals treated with halo-

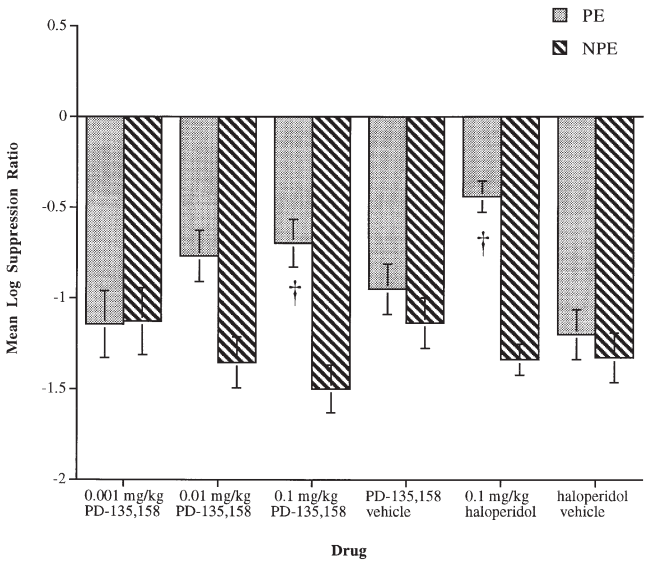

FIG. 1. Mean log suppression ratios of the preexposed (PE) and nonpreexposed (NPE) under six drug conditions: 0.001 mg/kg PD-135,158; 0.01 mg/kg PD-135,158; 0.1 mg/kg PD-135,158, PD-135,158 vehicle; 0.1 mg/kg haloperidol; and haloperidol vehicle. Significant values refer to comparisons with nonpreexposed counterparts ($^{\dagger}p < 0.01$).

peridol vehicle exhibited a suppression in drinking behavior that was similar to their NPE counterparts.

There is evidence, primarily from electrophysiological studies, to show that CCK_B antagonists have antipsychotic action. These compounds, similar to conventional antipsychotics (3), reduce DA activity in the substantia nigra and VTA (22,23,25). CCK_B antagonists differ, however, from conventional neuroleptics in several respects. First, they can inhibit DA activity after either acute or chronic administration, indicating an immediate onset of action (21). Second, CCK_B antagonists do not produce catalepsy, a behavioral indicator of extrapyramidal side effects (23). Clearly, CCK_B antagonists, in altering dopaminergic activity, are doing so in a way that is markedly different from conventional antipsychotics.

Despite the above findings, in classical animal models thought to be predictive of antipsychotic activity (e.g., conditioned avoidance responding or reversal of apomorphine- or amphetamine-induced locomotor activity) CCK_B antagonists were not active (21). Given that these behavioral paradigms may be sensitive only to dopaminergic antagonistic activity, such findings are hardly surprising. CCK analogues have, however, been tested using another animal model of the proposed cognitive deficiences in schizophrenia, namely prepulse inhibition (PPI). This model, similar to LI, has been shown to possess strong overall validity (31). Recently, and despite findings from another group (10) that CCK potentiates apomorphine-induced PPI deficits, Rasmussen et al. (26) have shown that the CCK_B antagonist LY288513 fails to block apomorphine-induced disruption of PPI. Nevertheless, we believe that the facilitation of LI by PD-135,158, as demonstrated here, is further evidence of LI as a model capable of detecting antipsychotic potential in compounds with differing modes of action.

While in this study PD-135,158 demonstrates an antipsychotic-like behavioral profile, the possibility exists that CCK's role in modulating emotional behavior (15) might be influencing the development of LI. CCK_B antagonists also exhibit anxiolytic (37) and analgesic (49) properties that could affect CER acquisition. However, this does not appear to be the case, because PD-135,158 did not affect suppression in any of the NPE groups.

The extent to which one can draw any conclusions about the effects of CCK_B antagonists on LI may be limited by the fact that the compound tested here is only one of a number of structural classes of CCK_B antagonist that have been developed. Structurally, PD-135,158, is derived from CCK itself, making it part of a group of CCK antagonists known as peptoids. There are other types of antagonists that are chemically quite distinct from each other, such as the benzodiazepine analogues and amino acid derivatives (15). Whether or not the peptoid class acts through the same neural substrates as other types of CCK_B antagonists remains to be ascertained. Indeed, even for those compounds with similar structures there might be subtle differences in any pharmacological effects (24). In one study, Meltzer et al. (19) found that, unlike other CCK_B antagonists, PD-134308 (another peptoid) did not alter the spontaneous activity of substantia nigra or VTA DA cells. Clearly, then, there is a need to test the effects of other CCK_B antagonists, from diverse structural classes, on the development of LI.

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