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Antipsychotic Potential of CCK-Based Treatments:

An Assessment Using the Prepulse Inhibition Model of Psychosis

David Feifel, M.D., Ph.D., Tammi Reza, and Stephanie Robeck

Systemic injections of cholecystokinin (CCK), a "gut–brain" peptide, have been shown to modulate brain dopamine function and produce neuroleptic-like effects on such dopamine-regulated behaviors as locomotor activity. However, clinical trials of CCK agonists in schizophrenia patients showed mixed results. To re-examine the antipsychotic potential of CCK-based treatments, we examined systemic injections of CCK analogs in an animal model with strong face and construct validity for sensorimotor-gating deficits seen in schizophrenia patients and with strong predictive validity for antipsychotic drug activity. Prepulse inhibition (PPI) occurs when a weak acoustic lead stimulus ("prepulse") inhibits the startle response to a sudden loud sound ("pulse"). PPI is significantly reduced in schizophrenia patients and rats treated with dopamine agonists. Antipsychotics reverse decreased PPI in rats to a degree highly correlated with their clinical efficacy. Subcutaneous (SC) injections of caerulein (10 μg/kg) a mixed $CCK_{A/B}$ agonist, partially reversed amphetamine-induced reduction of PPI; whereas, SC haloperidol (0.5 mg/kg) totally reversed amphetamine-induced disruption of PPI. Caerulein's effect on PPI was blocked by pretreatment with a CCK_A antagonist (devazepide) but not a CCK_B antagonist (L-365,260). CCK-4, a preferential CCK_B agonist, had no significant effect on PPI. These results suggest that caerulein produces a weak neuroleptic-like effect on PPI that is mediated by stimulation of CCK_A receptors. Possible circuities in this effect are discussed. In a separate experiment, SC caerulein produced to a more potent neuroleptic-like profile on amphetamine-induced hyperlocomotion, suggesting that selection of preclinical paradigms may be important in evaluating the antipsychotic potential of CCK-based treatments.
[Neuropsychopharmacology 20:141–149, 1999]

KEY WORDS: *CCK; Dopamine; Sensorimotor gating; Prepulse inhibition; Schizophrenia*

Cholecystokinin (CCK) is a peptide that acts in the brain as a neurotransmitter and may play an important role in regulating several important aspects of brain function, including sleep (Mansbach and Lorenz 1983), appetite (Lee et al. 1994), anxiety (Csonka et al. 1988), and seizure activity (Zhang et al. 1996). Behavioral, neurochemical, and electrophysiological studies, have demonstrated that CCK can modulate dopamine activity in the mesolimbic system where both known CCK receptor subtypes, CCK_A and CCK_B, have been identified (for review see Crawley 1991). This has led to speculation that CCK may play a role in the pathophysiology of schizophrenia (Nemeroff and Bissette 1992; Nair et al. 1986). Support for this has come from studies showing

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Received 13 November 1997; revised 23 February 1998; accepted 1 April 1998.

Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010
0893-133X/99/$–see front matter
PII S0893-133X(98)00041-4

significantly lower CCK levels in the cerebrospinal fluid (Beinfeld and Garver 1991; Verbanck et al. 1984) and postmortem brains (Schalling et al. 1990) of drug-free schizophrenia patients as compared to matched controls.

Systemic administration of CCK analogs in rats have been shown to modify behavior (Van Ree et al. 1983; Nair et al. 1986) and brain function (Kihara et al. 1992, 1993) in a manner consistent with a neuroleptic-like action. For example, systemically administered CCK agonists block amphetamine-induced hyperlocomotion (Crawley et al. 1981; Van Ree et al. 1983; Vasar et al. 1991) and modulate central dopamine turnover (Kihara 1992, 1993). Based upon these findings, the effects of systemically administered CCK analogs in schizophrenia patients were examined in a series of clinical trials (reviewed in Nair et al. 1986 and Albus 1988). Preliminary, uncontrolled trials suggested that such nonselective CCK agonists as caerulein had significant antipsychotic properties (Itoh et al. 1982; Moroji et al. 1982; Nair et al. 1982). However, subsequent placebo-controlled studies were equivocal, with some investigators (Nair et al. 1984; Van Ree et al. 1984), but not others (Lotstra et al. 1984; Hommer et al. 1985; Tamminga et al. 1986; Peselow et al. 1987) finding significant antipsychotic effects.

The discrepancy between the positive preclinical findings and the equivocal clinical studies examining the antipsychotic properties of CCK may be related to problems associated with preclinical modeling of schizophrenia. Much of the evidence for antipsychotic effects for CCK comes from locomotor-based paradigms. However, CCK produces strong effects on operational measures of anxiety (Csonka et al. 1988) and arousal (Mansbach and Lorenz 1983) that are likely to effect locomotor activity, although they may not be directly related to antipsychotic effects. To re-examine the antipsychotic potential of systemically administered CCK treatments, we used a nonlocomotion-based animal model that exhibits strong face, construct, and predictive validity to information processing deficits present in schizophrenia patients.

Prepulse inhibition (PPI) is an operational measure of sensorimotor gating. PPI occurs when the startle response to a sudden intense stimulus such as a loud noise ("pulse") is inhibited by a weak lead stimulus (e.g., sound), presented 30 to 200 msec prior to the startling stimulus ("prepulse") (Graham 1975). PPI is a stable phenomenon across a wide number of species, including humans (Schwarzkopf et al. 1993) and rats (Swerdlow et al. 1994) using similar parameters. PPI is deficient in schizophrenia patients (Braff and Geyer 1990) and schizotypal patients (Cadenhead et al. 1993) who are not on antipsychotic medication. This is thought to be an expression of the deficits in the "filtering" or "gating" of environmental information that frequently has been described as an important clinical dimension in schizophrenia (Braff and Geyer 1990; McGhie and Chapman 1961). Supporting an association between sensorimotor gating deficits and clinical manifestations of schizophrenia is the finding that schizophrenia patients with maximal PPI deficits show the greatest thought disorder (Butler et al. 1991). PPI also correlates inversely with measures of psychosis proneness in college students (Schell 1995).

Mesolimbic dopamine regulates PPI (Swerdlow et al. 1992; Mansbach et al. 1988). In animals, PPI is disrupted by such direct and indirect dopamine agonists as amphetamine and apomorphine (Mansbach et al. 1988). Both typical and atypical antipsychotic agents tend to normalize PPI deficits in rats treated with dopamine agonists, an effect significantly correlated with their clinical efficacy ($r = 0.96$) (Swerdlow and Geyer 1993; Swerdlow et al. 1994). Thus, PPI represents both a valuable model for the study of neurobiological substrates of schizophrenia and a highly predictive preclinical screen for novel antipsychotics. We have recently demonstrated that CCK-8 administered into the nucleus accumbens potentiates apomorphine-induced disruption of PPI (Feifel and Swerdlow 1997).

The purpose of the current study were to threefold. First, to evaluate the antipsychotic potential of systemically administered caerulein, a mixed $CCK_{A/B}$ agonist using a PPI model of psychosis. Second, to determine the CCK receptor pharmacology of carulein's effects by comparing them to the PPI effects of a preferential CCK_B agonist, $CCK_{30–33}$ (CCK-4) and by examining the effects of pretreatment with selective CCK_A and CCK_B antagonists. A third purpose was to compare caerulein's effects in the PPI paradigm to its effects on a more commonly used locomotor-based model of psychosis. Subcutaneous haloperidol was also tested and used as a reference for neuroleptic actions on PPI.

METHOD

Subjects

Male Sprague–Dawley rats (225–250 g on arrival) were housed in groups of two or three and maintained on a reversed 12:12 hour light/dark schedule (lights on at 0700 h), with food and water provided ad libitum. Behavioral testing occurred between 0900 and 1500 h, beginning 7 days after introduction of rats to their cages. Animals were handled individually within three days of arrival.

Drugs

Fresh drug was weighed out and prepared on each test day. Caerulein, CCK4, d-amphetamine and haloperidol were each dissolved in 0.9% saline. Devazepide (L,364-

718) and L-365,260 (generous gifts of Dr. Missaghi, Merck Sharp-Dohme) were dissolved in DMSO and saline. Control treatments for these compounds consisted of the corresponding vehicle alone. All drugs were injected subcutaneously (SC). CCK antagonists, when tested, were always injected 30 min prior to startle testing. CCK agonists were always injected 15 min before testing, and amphetamine was injected 10 min prior to startle testing. Each drug solution was diluted so that SC injection volumes remained constant at 1 ml/kg.

Behavioral Testing

For PPI testing, animals were placed in separate startle chambers (SR-LAB, San Diego Instruments, San Diego, CA, USA) which consisted of a Plexiglas cylinder 8.2-cm in diameter resting on a 12.5 × 25.5 cm Plexiglas frame within a ventilated enclosure housed in a sound-attenuated room exposed to a 65 dB background noise. Following a 5-min acclimation period, acoustic noise bursts were presented via a speaker mounted 24 cm above the animal. A piezoelectric accelerometer mounted below the Plexiglas frame detected and transduced the motion within the cylinder. Startle amplitude was defined as the degree of motion detected by this accelerometer. Rats were exposed to five different stimuli conditions: no stimulation; 120-dB startle pulse alone (P-Alone); and 120-dB startle preceded by a 3-, 5-, or 10-dB acoustic prepulse, administered 100 ms before startle. Stimuli were presented in five blocks, arranged in a pseudorandomized order. There were an average of 15 s between stimuli. For locomotor measurements, rats were placed in individual cages equipped with a series of horizontal infrared beams to record activity (San Diego Instruments, San Diego, CA, USA).

Statistical Analyses

Prepulse inhibition was calculated as the startle amplitude following prepulse conditions as a percentage of startle amplitude under pulse-only conditions using the following formula, [1 − (prepulse/pulse-only)] × 100. Analysis of data was then carried out using a three-factor ANOVA in which CCK analogs or haloperidol was a between factor; whereas, amphetamine condition and prepulse intensity were within factors. Significant factor results from the ANOVA were followed up with post-hoc comparisons of individual group means using Students *t*-tests with Bonferonni correction for multiple comparisons. Because prepulse intensity did not significantly interact with any other factors, PPI averaged over the three prepulse intensities is reported here.

For locomotion, both cumulative activity counts and cross-over counts were collected for a period of 20 minutes beginning 5 minutes after rats were placed in cages. Results were analyzed using a two-way ANOVA (caerulein dose × amphetamine condition), because this time period corresponded to the time period of PPI measurements made in startle chamber. Because both activity counts and cross-over counts showed similar trends only activity counts are reported.

Experiment 1: Effects of SC Caerulein, CCK4 and Haloperidol on PPI

Drug-naive rats were given SC injections of either caerulein (0, 1, 10 or 100 μg/kg), CCK4 (0, 5, 50 ,500 μg/kg) or haloperidol (0, 0.5 mg/kg). Immediately after these injections, animals were given a second SC injection consisting of either amphetamine (2 mg/kg) or saline. Animals were returned to their transport cages for 10 minutes and then placed in startle chambers for testing. Those animals that received amphetamine on the first test day received saline on the second test day and vice versa. The type and dose of CCK-agonist were kept constant on both test days.

Experiment 2: Locomotor Activity

A separate group of rats was given SC injections of caerulein (0, 1, 10 or 10 μg/kg) followed by amphetamine (2 mg/kg) and were then placed in locomotor cages (San Diego Instruments, San Diego, CA, USA). Each animal was tested on two occasions separated by at least 7 nontest days in a manner described in Experiment 1.

Experiment 3: The Effects of CCK_A and CCK_B Antagonists on Caerulein's PPI Effects

A separate group of drug-naive rats were used in this experiment. They were pretreated with one of four doses (0, 0.1, 1.0, 10 mg/kg) of either devazepide (L-364,718), a CCK_A receptor antagonist, or (L-365,260), a CCL_B receptor antagonist, injected SC 30 minutes prior to startle testing. Fifteen minutes later, they received a second SC injection of either caerulein (10 μg/kg) or saline, followed by third SC injection of amphetamine (2 mg/kg) or saline. Ten minutes following the last injection, animals were placed in startle chambers for testing. Rats in this study were tested only once.

RESULTS

Experiment 1

Caerulein. Figure 1 illustrates the effects of caerulein on PPI. Amphetamine produced a significant disruption of PPI ($F[1,30] = 57.5$, $p < .0001$). There was also a significant main effect of prepulse intensity on percent PPI whereby more intense prepulses produced greater PPI ($F[2,60] = 13.2$, $p < .0001$). There was also a significant main effect of caerulein that increased percent PPI

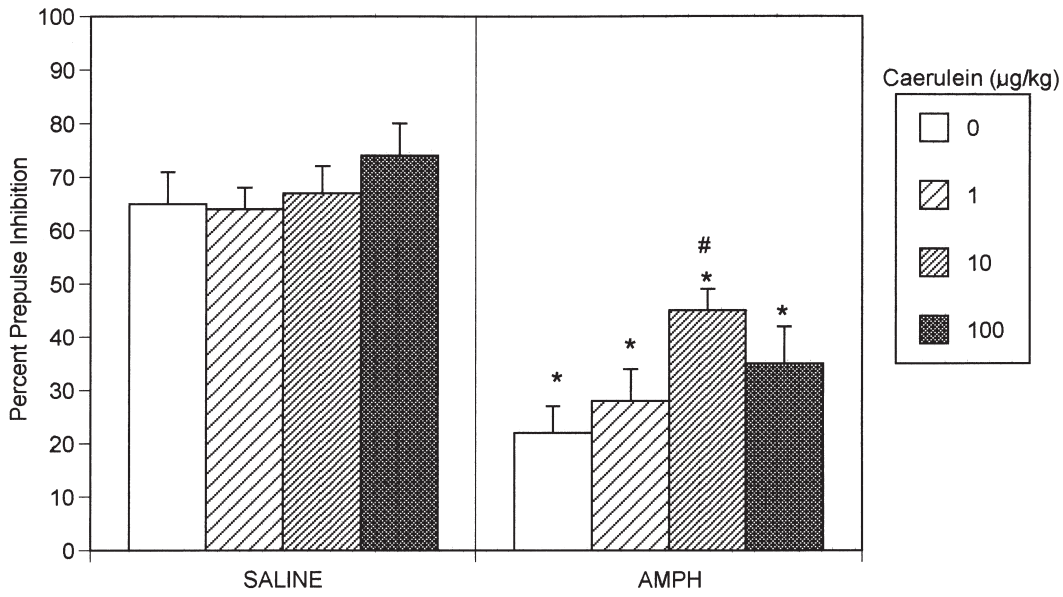

Figure 1. The effects of caerulein on PPI. Bars represents percentage prepulse inhibition (±SEM) averaged over all trials using three prepulse intensities (3, 5 and 10 dB) above background. * represents significantly different ($p < .05$) relative to treatments with same dose of caerulein but no amphetamine. # represents significantly different ($p < .05$) relative to 0 µg/kg caerulein/amphetamine group. The number of rats in each treatment group was 8 to 10.

(F[3,40] = 3.0, $p < .05$). There were no significant caerulein × amphetamine (F[3,30] = 0.1, NS), caerulein × prepulse intensity (F[6,60] = 0.5, NS), amphetamine × prepulse intensity (F[2,60] = 0.1, NS), or caerulein × amphetamine × prepulse intensity (F[6,60] = 1.1, NS) interactions (Table 1). Post-hoc comparisons revealed that no dose of caerulein had a significant effect on baseline PPI and that 10 µg/kg caerulein significantly increased PPI in amphetamine-treated rats relative to rats treated with amphetamine and saline. Pulse-alone startle amplitude was not significantly affected by amphetamine (F[1,30] = 0.6, NS), caerulein (F[3,30] × 2.1, NS) or an interaction between them (F[3,30] = 1.1, NS).

CCK4. Figure 2 illustrates the effects of CCK4 on PPI. Amphetamine produced a significant disruption of PPI (F[1,29] = 54.9, $p < .0001$). There was, once again, a significant main effect of prepulse intensity on PPI whereby more intense prepulses produced greater PPI (F[2,58] = 30.4, $p < .0001$). CCK4 did not have a significant overall effect on PPI (F[3,29] = 1.0, NS) and amphetamine × CCK4 (F[3,29] = 0.6, NS), AMP × prepulse intensity (F[2,58] = 2.9, NS), CCK4 × prepulse intensity (F[6,58] = 0.3 , NS) and CCK4 × prepulse intensity × amphetamine (F[6,58] = 0.4, NS) interactions were all nonsignificant (Table 2). Post-hoc comparisons reveal that 5 µg/kg CCK4 significantly potentiated amphetamine's effect on PPI. Pulse-alone startle amplitude was not significantly affected by amphetamine (F[1,29] = 1.7, NS), CCK4 (F[3,29] = 1.7, NS) or an interaction of the two (F[3,29] = 0.8, NS).

Haloperidol. Figure 3 illustrates the effects of haloperidol (0.5 mg/kg) on PPI. Amphetamine did not have a significant main effect on PPI (F[1,15] = 0.99, NS) and haloperidol's main effect on PPI approached significance (F[1,15] = 3.71, $p = .07$). There was, as usual, a significant effect of prepulse intensity (F[2,30]=10.7, $p < .001$). There was a significant amphetamine × haloperidol interaction (F[1,15] = 11.94, $p < .005$). However, amphetamine × prepulse intensity (F[2,30] = 0.16, NS), haloperidol × prepulse intensity (F[2,30] = 2.66, NS) and amphetamine × haloperidol × prepulse intensity (F[2,30] = 0.65, NS) interactions were all non significant. Post-hoc comparisons reveal that haloperidol reversed amphetamine-induced disruption of PPI.

Locomotor Activity. Amphetamine significantly increased locomotion (F[1,30] = 59.3, $p < .0001$) and caerulein had an significant overall inhibitory effect (F[3,30] =

Table 1. Startle Response following Caerulein Injections

Caerulein (µg/kg)	Saline		Amphetamine	
	P	**PP + P**	**P**	**PP + P**
0	389 ± 95	253 ± 74	356 ± 66	78 ± 13
1	268 ± 45	172 ± 31	325 ± 54	94 ± 17
10	261 ± 34	177 ± 28	247 ± 23	111 ± 15
100	290 ± 34	215 ± 38	180 ± 57	63 ± 15

Values represent mean startle amplitude (±SEM) following pulse alone (**P**) and prepulse-pulse (**PP + P**) presentations.

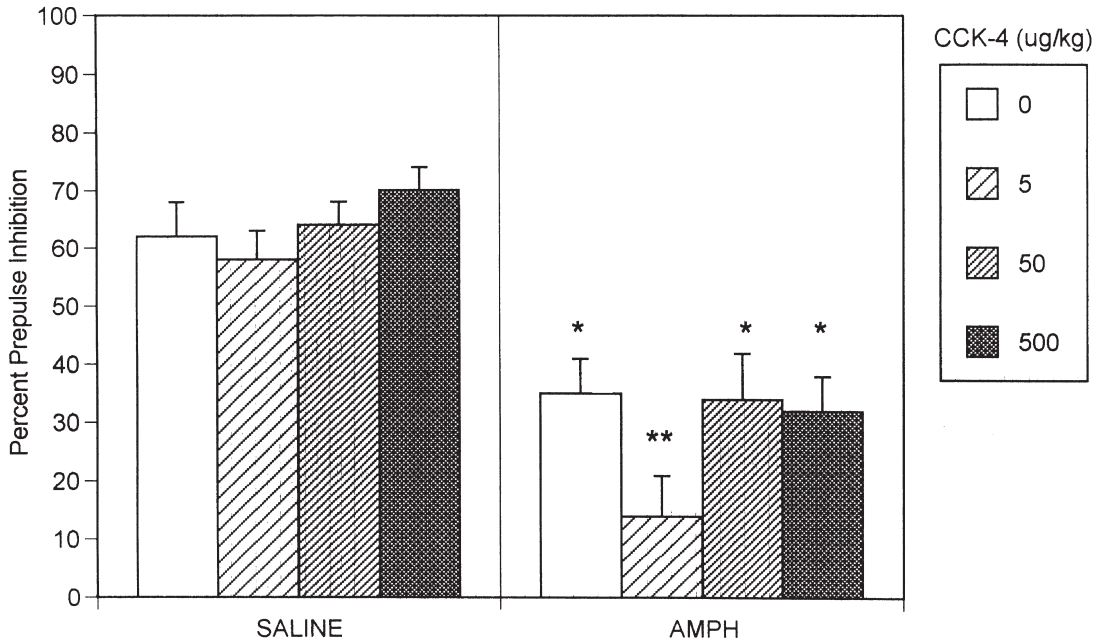

Figure 2. The effects of CCK-4 on PPI. Bars represents percentage prepulse inhibition (±SEM) averaged over all trials using three prepulse intensities (3, 5 and 10 dB) above background. * represent significant difference from (* = $p < .05$, ** = $p < .01$) relative to treatments with the same dose of caerulein but no amphetamine. The number of rats in each treatment group was 8 to 9.

4.89, $p < .01$) on locomotion. There was no significant interaction of caerulein × amphetamine (F[3,30] = 1.69, $p <$ NS). Figure 4 illustrates the locomotor results for the 20-minute interval after drug administration that corresponds with PPI testing. Post-hoc analysis indicates that, during this period, all doses of caerulein significantly decreased locomotion in amphetamine-treated animals and that 100 μg/kg caerulein also significantly decreased spontaneous locomotion.

CCK-Antagonists. Figure 5 illustrates the effects of combined CCK antagonist and caerulein injections on PPI. Devazepide (F[3,29] = 3.21, $p < .05$) but not L-365,260 (F[3,30] = 1.21, NS) had a significant effect on PPI. Post-hoc comparisons indicate that all doses of devazepide blocked caerulein's antiamphetamine effect on PPI, and the highest dose of devazepide (10mg/kg) potentiated amphetamine's effect on PPI (Table 3). In contrast low doses of L-364,718 produced a nonsignificant tendency to increase caerulein's antiamphetamine effect on PPI.

Table 2. Startle Response following CCK-4 Injections

CCK-4 (μg/kg)	Saline		Amphetamine	
	P	PP + P	P	PP + P
0	384 ± 64	238 ± 56	296 ± 57	107 ± 26
1	382 ± 52	222 ± 42	307 ± 69	43 ± 17
10	272 ± 57	171 ± 34	229 ± 50	80 ± 20
100	435 ± 78	305 ± 54	350 ± 64	122 ± 23

Values represent mean startle amplitude (±SEM) following pulse alone (**P**) and prepulse-pulse (**PP + P**) presentations.

DISCUSSION

Consistent with previous reports, 1 to 10 μg/kg of SC caerulein was able to prevent amphetamine-induced hyperlocomotion, and high doses decreased spontaneous motor activity (Crawley et al. 1981; Van Ree et al. 1983; Vasar et al. 1991). This is consistent with a neuroleptic-like effect. Caerulein's effect on PPI was far less potent. Caerulein displayed an inverted-U shaped dose-response relationship similar to other reports of its effect on behavior (Itoh et al. 1992; Masuda et al. 1992). Only the 10 μg/kg dose of caerulein was able to increase amphetamine-reduced PPI significantly. However, in contrast to haloperidol, none of the doses of caerulein fully reversed amphetamine-induced reduction in PPI or significantly altered baseline PPI. Caerulein's effects on PPI, therefore, suggest a weaker neuroleptic-like action than do its locomotor effects. A similar partial neuroleptic-like effect of PPI was demonstrated by caerulein in the two separate experiments reported here (Experiments 1 and 3), although the degree of PPI reduction produced by amphetamine alone in the two experiments differed markedly (22% vs. 45%). Caerulein's PPI effects in this study are more consistent, than are the locomotor results, with the equivocal re-

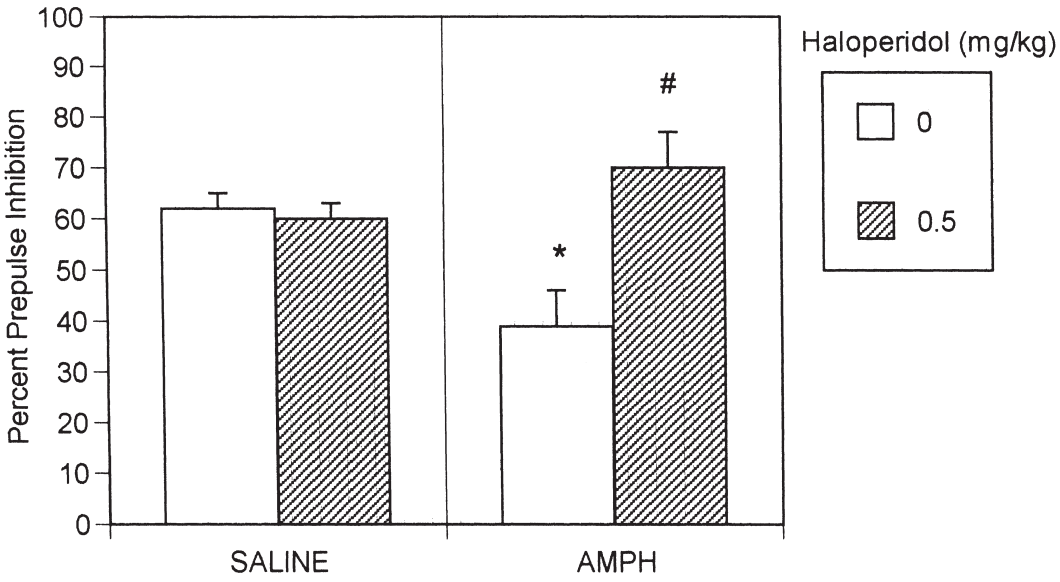

Figure 3. The effects of haloperidol on PPI. Bars represents percentage prepulse inhibition (±SEM) averaged over all trials using three prepulse intensities (3, 5 and 10 dB) above background. * = significantly different ($p < .05$) relative to saline/saline treatment condition, and # is significantly different ($p < .05$) relative to treatments with same dose of amphetamine but not haloperidol. The number of rats in each treatment group was 7 to 10.

sults of clinical trials conducted using caerulein in schizophrenia patients. This suggest that PPI may posses stronger predictive validity for CCK's putative antipsychotic activity than locomotor-based animals models.

Because CCK-4, a preferential CCK_B receptor agonist, did not display any neuroleptic-like effects on PPI, it is likely that the weak neuroleptic-like effect produced by SC caerulein is mediated by CCK_A receptors. CCK-4 actually displayed a nonsignificant tendency to potentiate amphetamine's action at the lowest dose tested (5 μg/kg), which is the same dose-range in which caerulein displays its weak neuroleptic-like effects. It is possible, therefore, that mixed CCK agonists produce simultaneous and opposing modulation of am-

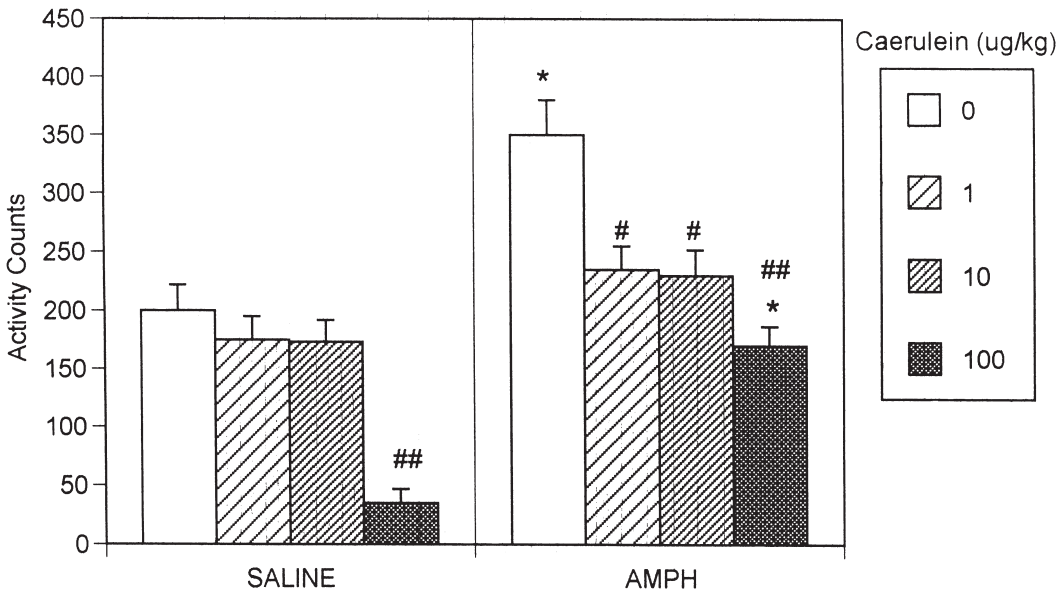

Figure 4. The effects of caerulein locomotion. Bars represents locomotor activity counts (±SEM) for a 20-minute period after drug administration. * represents significantly ($p < .05$) relative to treatments with same dose of caerulein but no amphetamine. # represents significantly different (# = $p < .05$, ## = $p < .01$) relative to 0 μg/kg caerulein and same amphetamine condition. The number of rats in each treatment group was 8 to 10.

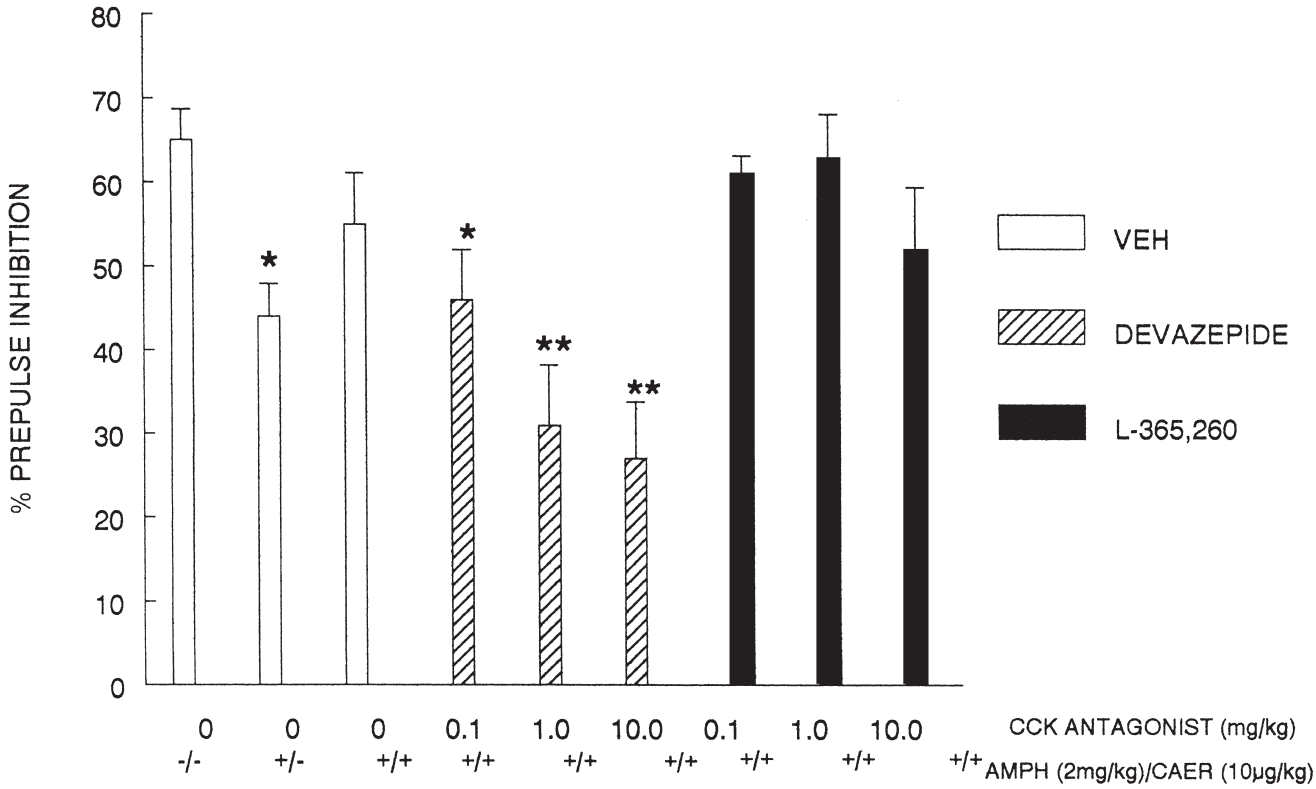

Figure 5. The effects of CCK antagonists on caerulein's PPI effects. Bars represent percentage prepulse inhibition (±SEM) averaged over all trials using three prepulse intensities (3, 5, and 10 dB) above background. * represents significantly different (* = $p < .05$, ** = $p < .01$) relative to vehicle/saline/saline treatment condition. The number of rats in each treatment group was 6 to 9.

phetamine-induced PPI deficits by concurrent activation of a CCK_A receptor-mediated, and a CCK_B receptor-mediated effect. This notion is given support by the results of combined injections of CCK antagonists and caerulein. Devazepide (L-364,718) not only reversed caerulein's weak antiamphetamine effect, it also potentiated amphetamine's effect of PPI at the highest dose (10 µg/kg). This may have occurred because the combined treatment with a CCK antagonist converted caerulein into a selective CCK_B agonist. The combination of L-365,260 and caerulein tended to have the opposite effects. At lower doses of L-365,260, caerulein's antiamphetamine effect was potentiated and amphetamine's effect on PPI was completely reversed, similar to haloperidol. This effect may be caused by the conversion of caerulein into a pure CCK_A agonist by simultaneous administration with L-365,260. Evidence from locomotor studies also suggest that systemically administered CCK agonists produce their neuroleptic-like effect via CCK_A receptors. Based upon these results, it is possible that selective CCK_A agonists may produce more potent antipsychotic-like effects following systemic administration than caerulein or other mixed CCK agonists. Relatively few experimental compounds have recently been proposed to act as selective CCK_A agonists, but they have not yet been extensively tested (Crawley and Corwin 1994).

Table 3. Startle Response following CCK Antagonist plus Caerulein Injections

	P	PP + P
SAL/SAL/VEH	294 ± 64	188 ± 41
SAL/AMPH/VEH	247 ± 73	111 ± 22
CER/AMPH/VEH	244 ± 63	137 ± 25
CER/AMPH/DEV (0.1 mg/kg)	207 ± 55	98 ± 18
CER/AMPH/DEV (1.0 mg/kg)	291 ± 71	93 ± 29
CER/AMPH/DEV (10 mg/kg)	236 ± 42	90 ± 24
CER/AMPH/L365260 (0.1 mg/kg)	184 ± 48	116 ± 14
CER/AMPH/L365260 (1.0 mg/kg)	204 ± 52	131 ± 26
CER/AMPH/L365260 (10 mg/kg)	246 ± 60	130 ± 29

Values represent mean startle amplitude (±SEM) following pulse alone (**P**) and prepulse-pulse (**PP** + **P**) presentations.

Central CCK-A receptors are believed to produce a potentiation of dopamine activity, and central CCK-B receptors are believed to produce antidopamine effects (Crawley 1991; Vaccarino 1994). This is supported by the finding that direct infusion of CCK into the nucleus accumbens produced a potentiation of dopamine agonist-induced disruption of PPI (Feifel and Swerdlow

1997). The putative CCK-A and CCK-B mediated effects on PPI seen in this study after systemic administration of caerulein are opposite to what would be expected from direct activation of CCK-A and CCK-B receptors in the mesolimbic system. This suggests that the weak neuroleptic-like effects of PPI seen after systemic administration of caerulein does not occur by direct stimulation of these mesolimbic receptors. It is possible, however, that systemically administered caerulein modulates the central substrates of PPI by stimulation of CCK receptors in the periphery. For example, changes in behavior and dopamine release in the nucleus accumbens produced by systemic injections of caerulein are abolished by bilateral subdiaphragmatic vagotomy (Crawley et al. 1981; Kihara et al. 1993), suggesting that the vagus nerve, upon which CCK-A receptors exist, is important in mediating these effects. It is also possible that peripherally injected CCK agonists exert their effect on PPI via the nucleus tractus solitarius, which is a major brainstem relay for vagus nerve signals from the periphery to the brain and a site in which the blood–brain barrier is relatively deficient. Both CCK_A and CCK_B receptors have been identified in the nucleus tractus solitarius (Branchereau et al. 1992). A CCK dopamine containing pathway from the nucleus tractus solitarius to the nucleus accumbens has been identified (Wang et al. 1992) and may be the route by which peripheral injections of CCK analogs indirectly modulate mesolimbic dopamine and PPI. Support from this comes from the finding that ablation of this nucleus tractus solitarius abolishes the behavioral actions of peripherally administered CCK (Crawley and Schwaber 1983).

In summary, systemically administered caerulein seems to produce a partical neuroleptic-like action in an amphetamine-disrupted PPI model of psychosis that is generally weaker than the antipsycholtic-like action produced in an amphetamine-induced hyperlocomotion model. This effect seems to be mediated by CCK_A receptors and may be opposed by concurrent proamphetamine effects produced by stimulation of CCK_B receptors.

ACKNOWLEDGMENTS

This research was supported by a National Alliance for Research in Schizophrenia and Depression (NARSAD) Young Investigator Award to DF.

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