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Interactions of Naloxone and Haloperidol with Phencyclidine: Effects on Milk Intake[1]

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WAGNER, G. C., C. M. FRANKO AND A. TOMIE. *Interactions of naloxone and haloperidol with phencyclidine: Effects on milk intake.* PHARMAC BIOCHEM BEHAV **20**(3) 379–382, 1984.— Phencyclidine (PCP), naloxone and haloperidol were administered alone and in combination to rats trained to drink sweetened-condensed milk during a 20 min daily session. PCP (1.0–16.0 mg/kg) produced a dose-dependent decrease in milk intake. All doses of naloxone (0.1–16.0 mg/kg) produced approximately a 30% decrease in milk intake. Haloperidol (0.125 mg/kg) had virtually no effect on milk intake. When a dose of naloxone which reduced milk intake by approximately 30% (8.0 mg/kg) was administered as a pretreatment to the PCP, the PCP curve was shifted to the left (lowered) to that degree. When haloperidol (0.125 mg/kg) was administered as a pretreatment to the PCP, the PCP dose-response curve was shifted 1.5 fold to the right. These interactions are similar to those observed in other behavioral paradigms and are discussed in reference to PCP's actions as an indirect dopaminergic agonist.

Phencyclidine Haloperidol Naloxone Milk intake

PHENCYCLIDINE'S (PCP) behavioral effects appear to be mediated through CNS receptors (binding sites) (e.g., [13, 17, 21]) which may be located presynaptically on dopaminergic neurons [7]. The interaction of PCP with these receptor sites results in indirect dopaminergic agonist actions such as dopamine release [2] and/or blockade of dopamine reuptake [9]. Although there are some noteworthy exceptions [6,16], the unconditioned [8] and conditioned [18] behavioral effects of PCP are antagonized by dopamine receptor blockers. These latter observations are consistent with the hypothesis that PCP acts as an indirect dopaminergic agonist.

In addition to acting as an indirect dopaminergic agonist, there is some evidence that PCP interacts with opiate compounds [3, 5, 18]. Both unconditioned and conditioned behavioral effects of PCP are enhanced by naloxone [5,18]. Thus, in addition to (or, conceivably, because of) its action as an indirect dopaminergic agonist, it appears that PCP may also be interacting with the endogenous opiate system.

PCP, like other indirect dopaminergic agonists [11,19], has been shown to reduce food intake [20]. The following study was conducted in order to determine the effects of naloxone and haloperidol on PCP's milk intake disruptive tendencies. It was observed that PCP decreased milk intake in a dose-dependent manner and that naloxone pretreatment resulted in a shift to the left and haloperidol pretreatment resulted in a shift to the right in this dose-response curve.

METHOD

Subjects

Subjects were 14 male, Sprague-Dawley rats (Blue Spruce) weighing between 180–200 g at the start of the experiment. They were housed individually in suspended metal cages in a colony room with a 12 hour (on 0800 hr) light/dark cycle. The rats had free access to water (except during the daily sessions) and were food deprived starting 24 hours before experimentation began and then maintained as described below. Four subjects became ill during the course of the study and eventually died (three with a respiratory ailment and the fourth undiagnosed). As soon as it became apparent that these rats were ill they were dropped from the study.

Procedure

Rats were first weighed each day and then given 20 min access to sweetened-condensed milk (Borden Co.; diluted 2:1, water:milk). Milk intake was determined by weighing the bottle before and after each session. Immediately after each session rats were given approximately 7 g of standard chow (Purina Lab Chow). When a stable baseline of milk intake was established (less than 10% variation over at least three baseline days) 0.9% saline or PCP was administered IP 20 min prior to the session. Doses of PCP (range 1.0 to 16.0 mg/kg) were varied in a random manner until a complete

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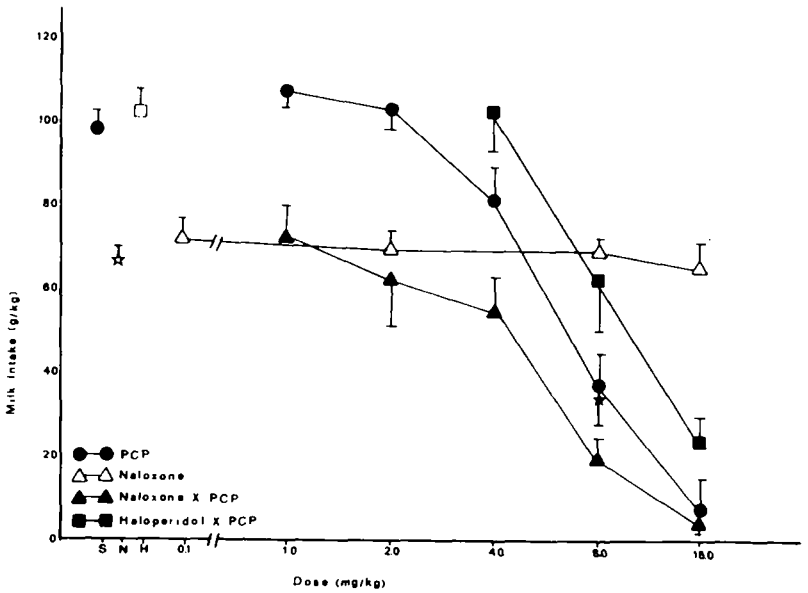

FIG. 1. Mean milk intake (± S.E.M.) expressed as g of milk per kg body weight as a function of dose of: phencyclidine (PCP); naloxone; PCP with naloxone (8.0 mg/kg) administered as a pretreatment; and, PCP with haloperidol (0.125 mg/kg) administered as a pretreatment. S=milk intake following injection of saline or the haloperidol vehicle. H=milk intake following injection of haloperidol (0.125 mg/kg). N=milk intake following injection naloxone (8 mg/kg; 40 min prior to the session) plus saline (20 min prior to session). The filled star over the 8 mg/kg dose represents the administration of that dose of PCP just prior to the determination of the PCP × haloperidol dose-response curve.

dose-response curve was determined. The PCP was administered no more often than every third day and only after a stable baseline intake was achieved.

When the PCP dose-response curve was completed, the procedure was repeated with naloxone (dose range 0.1 to 16.0 mg/kg) except that naloxone was administered SC 40 min prior to the milk session. Naloxone (8.0 mg/kg) was then administered in combination with the PCP; this dose of naloxone was administered SC 20 min prior to the PCP which, in turn, was given IP 20 min prior to the session. This procedure was repeated for all previously tested PCP doses. Finally, this procedure was repeated for haloperidol (0.125 mg/kg) and haloperidol in combination with PCP except that the haloperidol was administered IP 80 min prior to the milk (60 min prior to the PCP).

Throughout the study saline or the haloperidol vehicle were occasionally substituted in various combinations with the PCP, naloxone and/or the haloperidol injections. The choice of doses of naloxone (8.0 mg/kg) and haloperidol (1.25 mg/kg) as well as the pretreatment times for the drug interaction studies were based upon preliminary observations and a related study [18]. In addition, just prior to the determination of the PCP × haloperidol dose-response curve a test dose of 8 mg/kg PCP was readministered. The effects of this test dose (filled star, Fig. 1) was comparable to that of the initial determination, indicating that neither tolerance nor supersensitivity to PCP's effects were observed.

Drugs

Phencyclidine hydrochloride (supplied by NIDA) and naloxone hydrochloride (generously donated by Endo Labs) were dissolved in physiological saline such that the injection volume was always 1.0 ml/kg body weight. Haloperidol (generously donated by McNeil Pharmaceutical) was dissolved in 0.1 N acetic acid and then neutralized to pH 5.5 with sodium hydroxide to form a stock solution of 1.0 mg/ml. This stock solution was diluted (with saline) such that the final injection volume was 1.0 ml/kg body weight.

Data Analysis

The effects of variation in dose for each of the drug treatments on milk intake (expressed as g/kg body weight) were ascertained by repeated measures analysis of variance (ANOVA) using SAS-GLM procedure. Wilcoxon signed rank tests provided comparisons among the appropriate points. ED50 doses were estimated from the log (dose) linear (milk intake) plot of these functions with the saline dose considered as the 100% effect.

RESULTS

The administration of PCP (20 min prior to milk presentation) produced a dose-dependent decrease in milk intake. The ED50 for this effect was 7.0 mg/kg. Doses of naloxone (administered 40 min prior to milk) ranging from 0.1 to 16.8 mg/kg all produced approximately a 30% decrease in milk consumption. Finally, the administration of haloperidol at a dose of 0.125 mg/kg (80 min prior to milk presentation) had virtually no effect on milk intake (Fig. 1).

When naloxone (8.0 mg/kg) was administered as a pretreatment to the PCP, the PCP dose-response curve was shifted 1.6 fold to the left as indicated by the ED50 dose of 4.5 mg/kg. The PCP and the PCP × naloxone dose-response

curves were entered into a repeated measures 2×5 (treatment × dose) ANOVA which revealed significant main effects of treatment, $F(1,13)=20.74$, $p<0.01$, indicating that the difference between the heights of the curves is reliable, and of treatment × dose, $F(4,52)=3.57$, $p<0.05$, indicating that the difference in the slopes of the curves is reliable. Wilcoxon signed rank analyses revealed that for each of the four lower doses of PCP (1.0–8.0 mg/kg) there was a significant ($p<0.05$) decrease in milk consumption following naloxone pretreatment (Fig. 1).

When haloperidol (0.125 mg/kg) was administered as a pretreatment to the PCP the dose-response curve was shifted 1.5 fold to the right as indicated by the ED50 dose of 10.5 mg/kg. The PCP and the PCP × haloperidol dose-response curves were entered into a repeated measures 2×3 (treatment × dose) ANOVA which revealed a significant main effect of treatment, $F(1,9)=15.69$, $p<0.01$, indicating that the observed differences in the height of the curves was reliable but no significant main effect of treatment × dose, $F(2,18)=1.46$, $p>0.2$, indicating that the slope of the two curves was not significantly altered. Wilcoxon signed rank analyses revealed that for the two lower doses of PCP (4.0 and 8.0 mg/kg) there was a significant ($p<0.05$) increase in milk consumption following haloperidol pretreatment (Fig. 1).

Finally, neither saline nor the haloperidol vehicle produced a significant alteration in milk intake, nor was there any evidence for the devlopment of tolerance or supersensitivity to the milk intake decreasing effects of PCP over the course of the study (Fig. 1). [Note: (1) because the weight of the subjects increased over the course of the study, the data of Fig. 1 are reported in g/kg body weight. Milk intake (in g/kg) was stable for the duration of testing; (2) the shape of and relative positions of the dose-effect function of Fig. 1 are virtually identical whether the data are presented in g/kg or as a percent of each subject's baseline intake.]

DISCUSSION

PCP produced a dose-dependent decrease in milk consumption when it was administered 20 min prior to the session. This observation is consistent with that of others [20] who reported a dose-dependent decrease in milk intake when PCP was administered 15 min before the milk presentation. Thus, like other indirect dopaminergic agonists such as cocaine, amphetamine and methylphenidate, the acute administration of PCP reduces food intake [11,19].

Naloxone, like PCP, caused a reduction in milk intake. However, this effect was not dose dependent, but rather, doses over a 160 fold range all produced the same relative decrease in milk consumption. Decreases in milk [12] and food [4,14] consumption following naloxone administration have been previously reported. Furthermore, it is interesting to note that naloxone's consistent effect (over the dose range employed in the present study) has been previously observed [14]. Thus, rather low doses of naloxone are quite effective in reducing milk (food) intake, but the efficacy of naloxone is not then increased until extremely high doses (greater than 16.0 mg/kg) are administered.

When a dose of naloxone which reduced milk intake by about 30% was administered as a pretreatment to the PCP, the PCP dose-response curve was shifted to the left (more precisely, reduced) to that degree. Low doses of naloxone have been shown to enhance PCP's effects on unconditioned behaviors [5], PCP's rate-disruptive effect on schedule-maintained responding [18], and PCP's stimulus properties in the drug discrimination paradigm [15]. Opiate antagonists have also been shown to potentiate other dopaminergic agonists in both unconditioned and conditioned behavioral paradigms [1,10]. However, since the slopes of the PCP and the PCP × naloxone dose-response curves were different, a simple mechanistic interpretation of the interaction of these drugs at some opiate or non-opiate receptor is precluded.

When a dose of haloperidol which had negligible effects on milk intake was administered as a pretreatment to the PCP, the PCP dose-response curve was shifted to the right. Antagonism of PCP's effects by dopaminergic receptor blockers has been previously reported (e.g., [8,18]). Such observations are consistent with the hypothesis that PCP acts as an indirect dopaminergic agonist.

In summary, PCP produced a dose-dependent decrease in milk intake, an effect which was additive with naloxone and antagonized by haloperidol. These observations are consistent with other reports which demonstrated similar interactions among these drugs, primarily with unconditioned behaviors such as locomotor activity and stereotypic behavior.

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