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The Effects of Phencyclidine on Fighting in Differentially Housed Mice

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WILMOT, C A , C VANDERWENDE AND M T SPOERLEIN *The effects of phencyclidine on fighting in differentially housed mice* PHARMACOL BIOCHEM BEHAV **28**(3) 341–346, 1987 —The effects of phencyclidine (PCP) on the fighting of individually housed male mice were examined (1) after different lengths (5–35 days) of individual housing, and (2) in mice of different ages (35, 70 or 170 days old) at the onset of individual housing Significant increases in the total time spent fighting in a 10-minute aggression test were observed at 19–21 and 32–35 days of individual housing with 1 25 mg/kg PCP and at 10 and 32–35 days with 2 50 mg/kg PCP Relative to control groups, the percentage of mice fighting after 19–21 and 32–35 days of individual housing was significantly decreased with 2 5 mg/kg At 1 25 mg/kg, PCP increased total fighting time and decreased the latency to the first fight in mice at 35 or 70, but not 170 days of age at the onset of individual housing No increases in motor activity in individually housed mice were recorded at these doses These results suggest that PCP may facilitate fighting in mice when individually housed for a minimum of 10 days

Phencyclidine Isolation-induced fighting Aggressive behavior Differential housing

THERE are numerous references to a psychotic and often violent state associated with acute and chronic phencyclidine (PCP) abuse [1, 3, 9, 23, 32, 33] Soon after the introduction of PCP as a novel anesthetic, its clinical use was restricted due to adverse affects of deliria and psychoses indistinguishable from schizophrenia [7, 15, 19, 22]. These observations led to the suggestion that the behavioral effects of PCP may be the basis for a useful animal model for psychotic disorders Although there are inevitable limitations in identifying behavioral characteristics of laboratory animals that are relevant to the thought disorders of psychosis, the unpredictable combativeness and violent behavior associated with acute PCP toxicity and PCP psychosis suggest that the study of the interactions of PCP and aggressive behaviors may be a reasonable approach

Behavioral effects of PCP have been studied in several laboratory animal models of aggressive behavior, such as the resident-intruder paradigm in mice or rats housed individually or in pairs [2, 29, 30, 35], footshock-induced fighting [4], fighting induced by REM (rapid-eye-movement) sleep deprivation [27], shock-induced target-biting by confined male mice [17] and muricide [27,29]. PCP increased the frequency of agonistic behaviors in naive rats [30] and REM-sleep deprived rats [27] Both increases [2,29] and no change [35] in the time spent fighting have been reported in the models using mice, depending on the dosage and the protocol utilized

In the present study, two parameters in the model of isolation-induced fighting in mice, the age at the onset of individual housing and the length of individual housing, were varied to compare the effects of PCP treatment on fighting. Since the interactions of PCP and fighting behavior may be better observed when less than a maximal response is seen in control groups [30], the objective of the first experiment was to determine the percentage of mice fighting and the time spent fighting in an aggression test in PCP-treated (1 25–2.50 mg/kg) and control groups after different lengths (5 to 35 days) of individual housing A maximal percentage of fighters is typically attained after 3–4 weeks of individual housing The second experiment compared PCP-treated (1.25 mg/kg) and control groups which had been individually housed for 35 days, starting at 35, 70 or 170 days of age The objective of the third experiment was to determine whether or not there was a correlation between motor stimulation by PCP and either the latency to fight or the time spent fighting.

METHOD

Differential Housing

CF-1 male mice were obtained from Charles River Breeding Laboratory, Wilmington, MA, at 28 or 56–60 days of age and housed in groups of 15–25 After a minimum acclimation period of 3 days, the mice were either individually housed in a separate isolation room in opaque boxes measuring 28×12 5×14 cm or maintained grouped (15–20 per box) in the colony room in boxes measuring 45×27×14 cm Food (Wayne Lab Blox) and water were continuously available Housing conditions were maintained at 23±2°C, 30–60% humidity and a 12 hr light-dark cycle with lights on at 6 a m All behavioral testing occurred in the isolation room. Within their home box, the grouped mice were adapted to the isolation room for a minimum of 1 hour before testing

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Fighting Behavior

Individually (IH) and group housed (GH) mice were observed for fighting behavior toward a conspecific olfactory-bulbectomized male, a stimulus mouse which will neither initiate a fight nor retaliate [6,8]. Following the placement of the stimulus mouse in the home cage of the test mouse, the latency (LAT) in seconds to the first fight and the total time spent fighting (TFT) in seconds were recorded in a test period of 10 minutes, unless otherwise indicated. The first fight was defined by a bout of persistent biting and chasing with a minimum duration of 5 seconds, a criterion that discriminated a "fight" from a brief bite/attack Fighting was initiated and terminated by the test mouse only. LAT and TFT were recorded by a single non-blind observer with strict adherence to the above criteria to maintain objectivity When observing GH mice for fighting, the test mouse was transferred to a test box equivalent in size to the home cage of the individually housed mouse Fighting tests were conducted between 12 and 3 p.m. Each test mouse was subjected to only one fighting test to avoid any learning or training effects of repeated experience The stimulus mice were used repeatedly, but only once on a given test day Denenberg *et al* [8] have shown that olfactory-bulbectomized mice reliably elicit fighting

Motor Activity

Immediately following injection, mice were placed individually on electromagnetic activity meters (Columbus Instruments, Model S, set at 12–20 μA to give equal sensitivity) Counts were recorded starting with the 5th minute after injection via an external counter located outside the testing room Mice from both housing conditions were tested on the same days, between 11 a.m. and 5 p.m., with doses and housing condition randomized. A 5 minute fighting test immediately followed the activity measurement

Drugs and Dosage

Phencyclidine HCl was obtained from the National Institute of Drug Abuse, Washington, D C. Doses, in terms of the salt, were administered intraperitoneally in a volume of 10 ml/kg from solutions freshly prepared with distilled water

Statistics

Statistics were calculated with the Statistical Analysis System (SAS, Version 82 4) produced by the SAS Institute, Cary, NC [31]. The General Linear Model Procedure (PROC GLM) was used for analysis of variance (ANOVA) for unbalanced experimental designs, followed by a 2-tailed Student's *t*-test. Pearson rank correlations were used to compare motor activity counts and fighting time. Chi square tests were used to determine significant differences in the number of fighters in control and PCP-treated groups. The accepted level for significance was $p<0.05$.

EXPERIMENT 1 EFFECTS OF PCP AT DIFFERENT LENGTHS OF INDIVIDUAL HOUSING

Method

CF-1 male mice, 32–35 days of age, were individually housed and tested for fighting with a stimulus mouse after 5, 10, 19–21 or 32–35 days of individual housing A total of 293 mice were used in this experiment, divided over 4 replications, each consisting of 59, 57, 81 and 96 mice respectively. The distribution of mice among the treatment groups in each replication is outlined in Table 1. In the first two replications, mice were individually housed for 10, 20–21 or 35 days The control groups consisted of an equal number of untreated and vehicle-treated mice A 10-minute fighting test started 12–15 minutes following 1 25 or 2 50 mg/kg PCP or vehicle, IP Untreated mice were weighed but not injected There were no significant differences between untreated and vehicle-treated groups in TFT, $F(5,39)=1.94$, $p<0.1089$, or in LAT, $F(5,39)=0.58$, $p<0.7121$. Therefore, the untreated and vehicle-treated mice were combined into a single control group In the second two replications, mice were individually housed for 5, 10, 19–20 or 32–33 days, and all control mice received vehicle injections In each replication mice were tested only once to avoid any effects of repeated experience.

TABLE 1

SUMMARY OF THE NUMBER OF MICE FIGHTING AND THE NUMBER OF MICE TESTED AFTER 5–35 DAYS OF INDIVIDUAL HOUSING

	No Fighting/No Tested Length of Individual Housing (days)			
Treatment Group	5	10	19–21	32–35
Control				
1	—	4/10	13/14	4/5
2	—	7/9	5/6	8/10
3	1/9	3/8	4/7	4/5
4	2/8	4/6	4/6	7/8
Sum	3/17	18/33	26/33	23/28
% Fighting	17 6	54 5	78 8	82 1
PCP 1 25 mg/kg				
1	—	2/5	4/7	2/3
2	—	4/5	5/6	4/5
3	1/8	2/8	5/7	2/3
4	0/8	5/9	5/6	4/8
Sum	1/16	13/27	19/26	12/19
% Fighting	6 3	48 1	73 0	63 2
PCP 2 5 mg/kg				
1	—	3/5	2/8	0/2
2	—	1/5	1/6	3/5
3	0/8	3/8	2/7	2/3
4	1/8	3/9	2/12	3/8
Sum	1/16	10/27	7/33*	8/18*
% Fighting	6 3	37 0	21 2	44 4

The above table represents the distribution of the number of mice in the 4 replications of Experiment I (—, Not tested)

*$p<0$ 05, with respect to control, Chi square test

Results

The data from the four replications are summarized in Table 1 and Fig. 1 Between 5 and 35 days of individual housing, the percentage of fighters in the control groups increased from 18 to 82% (Table 1), a similar increase was seen in the groups treated with 1 25 mg/kg PCP. However, in the groups with 2.5 mg/kg PCP after 19–21 and 32–35 days of individual housing, there were significantly fewer fighters relative to both the control and PCP-1.25 groups. Following

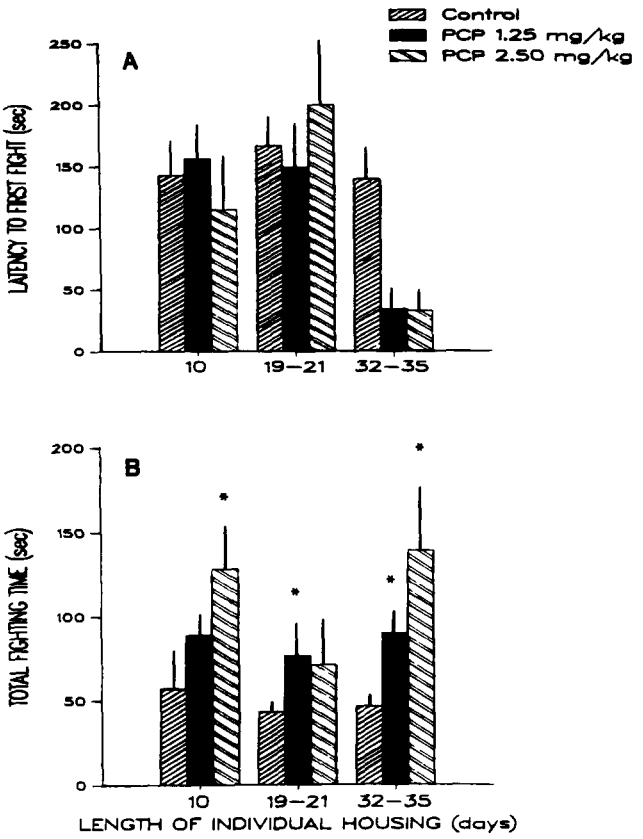

FIG 1 The effects of phencyclidine (PCP) on fighting in mice individually housed for 10, 19–21 or 32–35 days, starting at 32–35 days of age (1A) Latency to first fight (sec) and (1B) total fighting time (sec) in a 10 minute fighting test, starting 12–15 minutes after injection Mean±S E *$p<0$ 05, significantly different from respective control

the fighting test, the motor coordination of each mouse on a 45° inclined screen was observed for 15 seconds All mice with 1.25 mg/kg PCP and the majority with 2.5 mg/kg PCP displayed normal motor coordination on the inclined screen Some IH mice dosed with 2.5 mg/kg PCP were mildy ataxic, i.e. incoordinated on the inclined screen, and did not fight, representing 14, 10 and 6% of the mice receiving 2 5 mg/kg PCP at 10, 19–21 or 32–35 days of individual housing, respectively.

Both the length of individual housing and treatment had significant effects on the total fighting time in those mice fighting, $F(2,127)=5.13$, $p<0.0072$ and $F(2,127)=17$ 69, $p<0$ 001, respectively. No significant interaction occurred between length of individual housing and PCP, $F(4,127)=1.79$, $p<0$ 1356. As shown in Fig 1, 1.25 mg/kg PCP increased the total fighting time after 19–21 and 32–35 days of individual housing and 2.5 mg/kg PCP at 10 and 32–35 days

A noted difference in the quality of fighting of control mice and some of the mice injected with PCP after 32–35 days of individual housing was the persistence of biting attacks by PCP-treated mice toward a stimulus mouse displaying an upright or full submissive posture [14], frozen in a cataleptic state. In contrast, biting attacks by mice from control groups usually stopped or attenuated following the presentation of a submissive posture by the stimulus mouse

The F value from the 2-way ANOVA of the latency to the

TABLE 2

EFFECT OF PHENCYCLIDINE (PCP) ON THE NUMBER OF MICE FIGHTING WHEN INDIVIDUALLY HOUSED AT DIFFERENT AGES

Age	Number Tested	Number Fighting	Percent Fighting
35 days			
Control	20	16	80 0
PCP	11	8	72 7
70 days			
Control	18	13	72 2
PCP	10	8	80 0
170 days			
Control	19	1*	5 3
PCP	12	3*	25 0

Mice were individually housed for 32–35 days and injected with PCP, 1 25 mg/kg, or vehicle, IP, and observed for 10 minutes starting 12–15 minutes after injection *Significantly different from respective group at 35 or 70 days of age, Chi square test

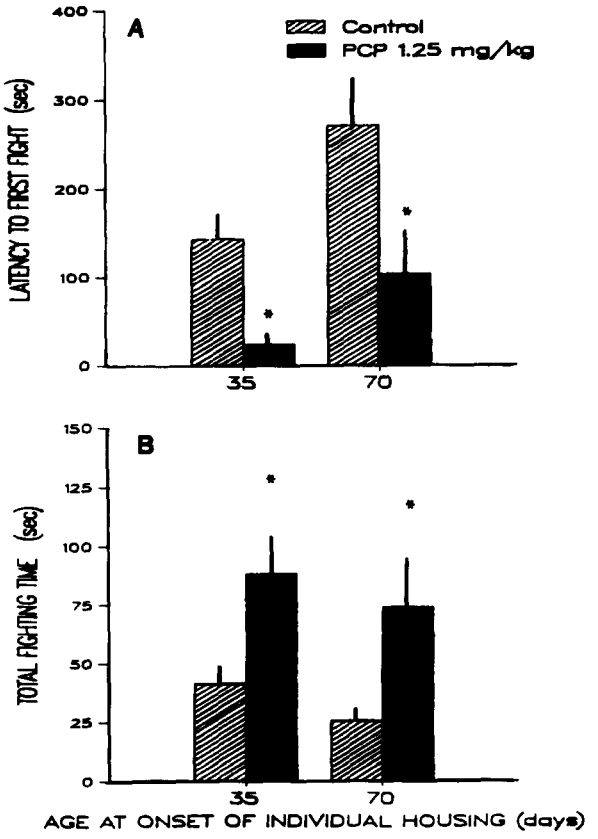

FIG 2 The effects of phencyclidine on fighting of mice individually housed at either 35 or 70 days of age Mice were tested after 32–35 days of individual housing (1A) Latency to first fight (sec) and (1B) total fighting time (sec) in a 10 minute fighting test, starting 12–15 minutes after injection Mean±S E. *$p<0$ 05, significantly different from respective control

TABLE 3

EFFECT OF PHENCYCLIDINE ON TOTAL FIGHTING TIME, LATENCY TO THE FIRST FIGHT AND MOTOR ACTIVITY IN GROUPED (GH) AND INDIVIDUALLY (IH) HOUSED MICE

Dose (mg/kg)	Activity Counts	Number Tested	Number Fighting	Latency to First Fight (sec)	Total Fighting Time (sec)
Control					
GH	76 ± 17	5	0	—	—
IH	216 ± 48‡	6	5	47 ± 13	47 5 ± 7 1
0 625					
GH	202 ± 34*	5	0	—	—
IH	172 ± 26	6	6	64 ± 29	50 2 ± 7 9
0 900					
GH	—	—	—	—	—
IH	224 ± 26	6	6	43 ± 15	100 2 ± 21 8
1 25					
GH	127 ± 21	5	—	—	—
IH	234 ± 45‡	6	6	78 ± 26	70 8 ± 20 9
1 75					
GH	—	—	—	—	—
IH	233 ± 22	5	5	40 ± 15	107 0 ± 20 0*
2 50					
GH	277 ± 41*	5	0	—	—
IH	278 ± 32	5	5	36 ± 10	130 1 ± 18 6†
5 00					
GH	373 ± 33†	5	1	32 0	24 4
IH	288 ± 117	3	0	—	—

Activity counts were recorded for 5 minutes, starting with the 5th minute after injection, mice were subsequently observed for fighting for 5 minutes starting with the 12th minute after injection Mean ± SEM (—, Not tested) *$p<0$ 05, †$p<0$ 01, significantly different from respective control, ‡$p<0$ 05, significantly different from Group Housed, Student's t-test

first fight did not meet the criterion for a significant overall effect, $F(8,127)=1$ 99, $p<0$ 0533, thus precluding F-tests for the main effects of length of individual housing and PCP However, a high proportion of PCP-treated mice at 32–35 days of individual housing initiated the first fight in less than 10 seconds, 58% and 50% for PCP-1 25 and PCP-2 5, in contrast to 9% of the mice in the control group.

EXPERIMENT 2 EFFECTS OF PCP IN MICE OF DIFFERENT AGES AT THE ONSET OF INDIVIDUAL HOUSING

Method

Mice of three different ages, 35, 70 or 170 days old, were individually housed for 32–35 days. The 28 mice in the 70-day-old group arrived from Charles River at 56 days of age The mice in the other two groups were from the same lot received at 28 days of age and group housed, 15–20 per cage in the colony room until individually housed at either 35 or 170 days of age. The different age groups were not tested for fighting on the same days Mice from all age groups were assigned to one of three treatment groups (1) no treatment, (2) vehicle (distilled water), or (3) PCP 1.25 mg/kg, with the following distribution· 35 days of age—(1) 10, (2) 10 and (3) 11, 70 days of age—(1) 9, (2) 9 and (3) 10, 170 days of age—(1) 9, (2) 10, and (3) 12 Stimulus mice were age-matched to the test mice

Results

In the mice individually housed at 35 or 70 days of age, there were no significant differences between the groups not treated and vehicle-injected in percentage of mice fighting (35 days of age 70% vs 90%, 70 days of age: 67% vs 78%), total fighting time (35 days of age, mean±S E . 32 4±5.8 vs. 48 5±11.8 sec, 70 days of age: 27.0±7.2 vs. 24 3±6 2 sec), or latency to the first fight (35 days of age 144±32 vs. 143±57 sec, 70 days of age 341±77 vs 189±57 sec). Of the mice individually housed at 170 days of age, one vehicle-treated mouse fought, and none of the untreated mice. The untreated and vehicle treated groups were combined into a single "Control" group for comparison to the group injected with 1 25 mg/kg PCP

In the control groups, 72–80% of the mice individually housed at 35 or 70 days of age fought, but only 5% of those individally housed at 170 days of age (Table 2) Only the mice from the 35 and 70 day age groups were included in the ANOVA The effects of PCP on both the total fighting time and the latency to fight were significant for both of these age

groups, $F(1,41)=4\ 10$, $p<0\ 0001$, and $F(1,41)=10.82$, $p<0\ 0021$, respectively (Fig. 2) The main effect of age was significant for latency to fight, $F(1,41)=5\ 60$, $p<0\ 0228$, but not for total fighting time, $F(1,41)=1.73$, $p<0\ 1958$ When individually housed at either 35 or 70 days of age, 1.25 mg/kg PCP increased the total fighting time and decreased the latency to fight Mice at 170 days of age were apparently less sensitive to the induction of fighting behavior by individual housing and not affected by PCP

EXPERIMENT 3 EFFECT OF PCP ON THE MOTOR ACTIVITY OF DIFFERENTIALLY HOUSED MICE

To determine if the increased fighting times observed with PCP were correlated to motor stimulation, motor activity was measured for 5 minutes preceding a 5-minute fighting test Mice 35 days old were either group housed or individually housed for 42–45 days PCP, 0 625–5 0 mg/kg, was administered 5 minutes prior to recording motor activity counts Activity counts were recorded from the 5th to 10th minute after injection, following which the mouse was transferred back to its home box. The fighting test started with the 12th minute after injection by placing the stimulus mouse in the box

In group housed mice, PCP produced a significant increase in motor activity, $F(4,23)=14.15$, $p<0\ 0001$ (Table 3) In contrast, no significant stimulation of activity over baseline was seen in individually housed mice, $F(6,31)=0\ 92$, $p<0\ 4951$. Vehicle-treated individually housed mice were more active than group housed mice Group housed mice were also tested for fighting following the motor activity measure. Only one mouse, treated with PCP 5 0 mg/kg, of the 28 group housed mice tested fought (LAT=32 sec, TFT=24.4 sec).

PCP had a significant effect in individually housed mice on the total fighting time, $F(5,27)=3\ 51$, $p<0.0142$, but not on the latency to fight, $F(5,27)=0.66$, $p<0.6571$ (Table 3) Preceding the aggression test with 5 minutes on the activity meter appeared to have a "priming effect " The difference in the handling of the mice prior to the aggression test may explain the discrepancy in the mean latency to fight from the two previous experiments. There was no apparent relationship between total fighting time and activity counts, Pearson rank correlation, $r=0\ 2339$

DISCUSSION

PCP in the dose range of 1 25 to 2.5 mg/kg PCP increased the time spent fighting in an aggression test by mice individually housed for at least 10 days, however the percentage of mice that fought was not increased above the 55–82% recorded in control groups housed in this manner These data suggest that PCP does not induce the animals to fight but rather may intensify that behavior when the subjects are already inclined to fight. This conclusion is supported by the fact that PCP was without effect in groups which exhibit a very low degree of fighting, such as in mice individually housed for 5 days or less, in mice individually housed at the age of 170 days or in mice that were group-housed. The observation that older animals were more resistant to the induction of fighting by individual housing is of interest. Similar effects of age at differential housing on the fighting of TO mice were reported by Goldsmith *et al.* [13]. These results suggest a decreased sensitivity of aged mice to the behavioral and neurochemical effects of individual housing.

The positive effect of PCP on fighting is limited to a narrow dose range. At 2.5 mg/kg, the number of mice fighting was significantly lower than the corresponding control groups at 19–21 and 32–35 days of individual housing, and yet there was a significantly greater mean total fighting time for the fighters The reduction in the number of fighters at 2.5 mg/kg was partially attributed to a reduced ability to initiate a fight as motor incoordination on an inclined screen was observed In those mice treated with 2 5 mg/kg which did not fight and were apparently unimpaired in motor function, it is possible that this dose approaches a threshold for disruption of fighting At the higher dose 5.0 mg/kg PCP, which produces significant motor stimulation [10, 11, 18, 25], neither after 11 days (8 mice tested, data not shown) nor after 45 days of individual housing (Table 3) were mice observed fighting. PCP-stimulated motor activity shows an inverted U-shaped dose-response curve in both rats [25] and mice [18], which is attributed to the onset of PCP-induced stereotypy and ataxia In an analogous manner, PCP-stimulated fighting may decline at higher doses which stimulate motor activity Takahashi *et al* [34] reported similar effects with ketamine, a ketone derivative of PCP In that study, 5 mg/kg ketamine significantly increased the time spent fighting with no effect on locomotion At higher doses, 10–45 mg/kg, which produced significant motor stimulation, no effects were seen on fighting time

The results of the present study and several others indicate that the effects of PCP on fighting will vary with dose, test situation and prior experience of the animal A common feature of the present study and two others [2,29] reporting that PCP increased aggression scores and attack-bite frequencies for mice individually housed is the lack of prior fighting experience of the test mouse In a study using fight-experienced paired (male-female) resident mice [35], PCP in a similar dose range did not increase attacks by the male resident mouse on the intruder. In naive rats, PCP increased the frequency of boxing episodes and offensive upright postures [30] Fight-experienced animals may be more attentive and responsive than naive animals to social cues, e g. submissive postures, which may inhibit further agression [14] In contrast, in naive animals PCP may interfere with the perception and association of these cues with submissive behavior. In this study PCP-treated mice frequently persisted in fighting after eliciting submission from the olfactory-bulbectomized mouse, whereas control mice typically stopped fighting

Since PCP is a potent motor stimulant [10,11], whether or not the increased fighting time was correlated to its motor stimulant effects was questioned. The relationship was tested by measuring both responses by each mouse in two sequential tests Activity counts did not correlate to the time spent fighting. Although a significant linear correlation between motor activity and attack-bite frequency with PCP, 1 0–3 0 mg/kg was reported in another study [2], an important distinction is that motor activity was assessed concurrently with fighting in [2], whereas they were not in the present study PCP produced a significant stimulation of motor activity of group-housed mice over baseline although it did not increase the tendency of group-housed mice to fight

The neurochemical mechanisms by which low doses of PCP increase fighting time are not known Many studies have reported altered serotonergic or catecholaminergic mechanisms in isolation-induced fighting [5, 16, 20, 24, 26, 28, 36]. Since fighting is a complex behavior integrating sensory input and emotional state to produce an organized site-directed motor output, it is not unexpected that other

neurochemical systems have been implicated as well. More recently it has been demonstrated that [3H]PCP binding sites can be differentiated from the sigma "opiate" receptor [12,21]. Whether or not the effects of PCP on fighting or the induction of fighting behavior by individual housing are mediated in part by these receptors is not known

In summary, these studies demonstrate that PCP may facilitate fighting in individually housed mice and that this effect is influenced by the duration of individual housing, the age of the mice when individual housing commences and the dose of PCP

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