Morphine-amphetamine-induced fighting and interim socialization*

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Traumatic and lethal fighting among male rats can be induced by a single moderate dose of amphetamine given during withdrawal from morphine. Socialization with other rats during the interval between terminal morphine and amphetamine modifies the course of subsequent aggressive behavior. Fighting is prolonged for rats maintained in isolation during the interdrug interval.

Thor & Teel (1968) and Thor, Hoats, & Thor (1970) have indicated that laboratory rats will exhibit aggressive behavior for extended intervals during withdrawal from previous morphine administration and that the extent and intensity of fighting is positively related to prior morphine dosage. D-amphetamine in moderate dosage, given during withdrawal from the narcotic drug etonitazene, potentiates fighting among grouped rats (Florea & Thor, 1968), and a single dose of amphetamine, given 90 h after withdrawal from morphine, stimulates traumatic fighting (Thor, 1969; in press). The present account describes replication experiments of drug-induced fighting with attention to social experience as a determinant of psychopharmacological response.

Vocalization was selected as a convenient and unambiguous response measure to continuously monitor fighting over an extended interval. According to Darwin (1872), vocal expression in a normally silent species is commonly associated with violent emotional outbursts. The loud and complex noise occasionally made by the wild or laboratory rat is thought to be an alarm or distress call and not in the normal repertoire of noises (Barnett, 1963). This unusually loud vocalization has been frequently noted in previous experiments as a distinctive component of violent fighting and is not heard between bouts of fighting or in the nonaggressive group situation.

EXPERIMENT 1

The first comparison was that of fighting in a group of drug-treated and socially exposed animals with fighting in a group of drug-treated animals lacking comparable social exposure. It was hypothesized that the housing of a strange S for 90 h in the home cage of a morphine-treated S would tend to inhibit later fighting when morphine-treated Ss were given a trigger dose of amphetamine and placed in a group

cage. Familiarity with the strange S was anticipated to generalize to other strange Ss and to restrain the intensity of fighting.

Subjects

Twenty-four hooded male rats (Long-Evans) from five litters were each isolated in separate cages after weaning at 25 days.

Procedure

Twelve Ss received daily intraperitoneal injections of morphine sulfate in gradually increasing dosage over 40 days to a maximum of 60 mg/kg/day. Six of the morphine-treated Ss (Group 1) remained in their cages after the terminal dose until receiving a single 2 mg/kg dose of d-amphetamine 90 h later. The remaining morphine-treated animals (Group 2) were each housed with one of the nonmorphine-treated isolates for 90 h. Remaining nonmorphine-treated isolates served as a control and simply remained in their separate cages (Group 3).

Ninety hours after the last morphine injection, the nontreated cohabitants in cages of Group 2 Ss were removed and discarded. All Ss (Groups 1, 2, and 3) then received a 2-mg/kg IP dose of d-amphetamine sulfate in distilled water. Within 30 min, each S was placed in his respective experimental group cage to measure and record intragroup fighting. Food and water were available throughout.

Apparatus

Each 30 x 30 x 20 cm fighting chamber was constructed of wood, Plexiglas, and acoustical tile. Vocal detection units were voice-operated relays (Eico) actuated by noise (90+ dB) to 7.6-cm tweeter loudspeakers mounted near the center of each cage ceiling. Contact closure of each relay actuated a pen on an Esterline-Angus event recorder. Each relay had its own power supply, and the recorder was transient suppressed with diodes to prevent false triggering. Calibration of sensitivity control on each voice-operated relay was conducted before and after the experiment. For previous application see Thor, Hoats, & Thor (1970).

Results

The recorded pips were totaled for each hour and are presented as cumulative frequency curves in Fig. 1.

Vocalization frequencies reflect the observed course of fighting. After termination of sustained hostility only minor and infrequent bouts of fighting occurred.

Fighting was prolonged in Group 1 (Ss had received both drugs and were isolated during the interim). Observations indicated agonistic behavior persisted for approximately 30 h in Group 1 and for only 7 h in Group 2. Occasional fighting responses occurred only during the first 4 h in Group 3.

Fighting was typical of that described for rats by Barnett (1963), Eibl-Eibesfeldt (1961), and Ulrich & Azrin (1962). Occasional bites were sustained by Ss in Group 3, but after 54 h all Ss appeared normal.

EXPERIMENT 2

Larger males were used in a modified replication study. Pretreatment with morphine was shortened to 5 days and a higher terminal dosage (200 mg/kg/day) was given. Number of cohabitant Ss during the interdrug interval was increased to four.

Subjects

Fifteen mature male hooded rats (Long-Evans) were assigned to three groups of five on the basis of weight. Mean weights were 330-340 g. All had lived in isolation from other rats since arrival from the supplier, 6 weeks prior to the study.

Procedure

Each S was given two daily IP doses of morphine sulfate in increasing dosage over 5 days to a maximum of 200 mg/kg/day. Individual doses increased from 20 mg/kg to 100 mg/kg in 20-mg/kg daily increments.

Each S in Group 1 received both drugs (2 mg/kg d-amphetamine) and no social experience during the 90-h interval between drugs. Group 2 was united immediately after the last morphine in a large group cage and was maintained in this cage for 90 h. Group 3 received both drugs in identical dosage to that given Group 1, but during the interdrug interval, each S was housed with four other male isolates. The experimental S and the four nondrug-treated cohabitants were all placed in a large group cage for 90 h. The weight of the cohabitants was within 50 g of the weight of the experimental S.

After receiving the amphetamine, each group was placed in one of the fighting chambers. Nondrug-treated cohabitants of Group 3 Ss were discarded.

Results

Vocalization was recorded for 54 h as in

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Fig. 1. (Above) Cumulative vocalization frequency as an index of group fighting behavior following one dose of amphetamine (2 mg/kg) given 90 h after terminal morphine (60 mg/kg/day).

Fig. 2. (Right) Vocalization frequency among groups receiving terminal morphine dosage of 200 mg/kg/day and 2 mg/kg trigger dose of amphetamine.

Experiment 1, and the resultant frequency data were plotted as a cumulative curve. Figure 2 describes the course of fighting as recorded for vocalization frequency over successive 1-h intervals.

Intense fighting during the first 6 h resulted in two deaths in Group 3 and one death in each of Groups 1 and 2. Expired Ss were immediately removed from the fighting chamber. One additional death occurred in Group 3 after approximately 40 h. Upon termination at 54 h, the greatest number of bite wounds were sustained by survivors in Group 3.

In contrast with Experiment 1, total vocalization was greater in Group 1 and more severe fighting was obtained in all groups.

EXPERIMENT 3

A third group comparison and modified replication introduced the following: (1) prewithdrawal morphine was reduced to 100 mg/kg/day, (2) the noncombatant cohabitants were carefully selected to be at least 100 g lighter in weight than the experimental Ss, and (3) disposition to fighting chambers and initiation of recording were accomplished as fast as possible (intensive fighting was observed in socialization groups of Experiment 2 beginning immediately after grouping).

Subjects

Fifteen male hooded rats (Long-Evans) were assigned to three groups with mean weights of 368, 370, and 374 g. Twenty smaller males were assigned to five groups of four each with mean weights of 262, 255, 245, 236, 215 g. All Ss were experimentally naive and had been living in separate cages since arrival from the supplier.

Procedure

Each experimental S (15 larger Ss) was pretreated with morphine sulfate over 5 days to a terminal daily dosage of 100 mg/kg. Individual bidaily doses increased from 10 to 50 mg/kg in 10-mg/kg daily increments.

Group 1 received no social experience during the interdrug interval of 90 h. Group 2 was brought together in a group cage for 90 h. Group 3 Ss were each housed with four smaller males for 90 h, with the largest S assigned to the cohabitant group with the greatest mean weight, etc.

The amphetamine injection of 2 mg/kg was administered to all Ss within 10 min, and recording was initiated within 2-3 min after groups were placed in the experimental cages.

Results

Some occasional fighting was observed

in social groups prior to amphetamine. However, the fighting among Groups 2 and 3 during the first hour of recording was notably more vigorous. Figure 3 describes the vocalization curves recorded and plotted as described in Experiments 1 and 2.

Original fighting during the first 2 h in Groups 2 and 3 accounts for nearly all the fighting observed or recorded as loud vocalization. During the first 10 min of recording, Group 2 made 576 vocal responses, Group 3 made 1,491 responses, and Group 1 made no response.

Fighting was lethal in Groups 2 and 3, with one death resulting in each group within 3 and 6 h, respectively. A second death occurred in Group 3 after 8 h. Although no deaths occurred in Group 1, extensive lacerations were noted, particularly in the facial area; two animals each lost one eye.

DISCUSSION AND CONCLUSIONS

The increase in the intensity of fighting in Experiments 2 and 3, compared to that of Experiment 1, may be due to the greater maturity of the Ss as well as to the increased terminal level of morphine administered. The comparable level of total vocalization reached by Group 1 in Experiments 2 and 3 indicates that the

Fig. 3. Vocalization frequency among groups receiving terminal morphine dosage of 100 mg/kg/day and 2 mg/kg trigger dose of amphetamine.

maturity of Ss is more significant than terminal morphine dosage; in each case the vocalization level is comparable, yet terminal morphine dosage was 200 mg/kg/day in Experiment 2 and 100 mg/kg/day in Experiment 3.

Fighting of Group 1 Ss (isolates) in all three experiments generated a comparable trend in the cumulative vocalization curves. Group 1 curves all indicate that approximately half of the total vocalizations occur during the first 10 h and that fighting terminates after 25-35 h. There was no comparable sustained fighting in any of the social groups (Experiments 1, 2, and 3) and, with the exception of Group 3 in Experiment 2, nearly all fighting and loud vocalization occurred during the first few hours after amphetamine.

The reversal in relative position of the Group 1 curve to that of Groups 2 and 3 when Figs. 2 and 3 are compared is the result of more rapid initiation of recording in Experiment 3. It may be noted that the change in relative position of the cumulative curves is dependent upon the high rate of vocalization in social groups during the first hour of recording in Experiment 3.

Severity of fighting in Experiments 2 and 3 was sufficient to result in permanent injury and death. Among all social conditions, the most severe fighting was observed in Group 3 during the first hour of recording. The turmoil of leaping and biting Ss was such that precautions were taken to avoid movement or tipping of the fighting chamber itself. Leaping Ss were observed bumping into the ceiling (30.5 cm high) of the cage.

Postmortem examination of Ss who expired during the recording interval

revealed no unusually severe bite wounds. Gross examination of internal state revealed no bleeding or wounds to vital organs. Appearance in fighting chamber prior to death was that of immobile withdrawal with absence of any response to the sporadic bouts of fighting among other Ss in the chamber. Death in absence of observed wounding following a fight between wild rats has been described by Barnett (1967).

In conclusion, socialization prior to amphetamine apparently reduced the duration of subsequent fighting but not the intensity of fighting immediately after grouping. Social experience with younger and smaller male Ss during the interim between morphine and amphetamine resulted in the most violent fighting.

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