Drug withdrawal and fighting in rats

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Rats were given the opioid drug etonitazene in drinking water on a schedule of increasing concentration to 90 mcg/ml. All animals then receiving dextroamphetamine injections during withdrawal exhibited vigorous, periodic fighting for 288 h post withdrawal.

Drugs obtained from opium produce withdrawal symptoms in rats (Martin et al, 1963) and a recent observation has described a behavioral concomitant of fighting when several rats simultaneously undergoing morphine withdrawal are placed in the same cage (Boshka et al, 1966). We have now repeatedly observed aggressive fighting in rats beginning three or four days after termination of morphine and continuing for several days. Extent of fighting is related to morphine dosage prior to withdrawal (Teel & Thor, 1967) with a terminal dosage of 400-600 mg/kg/day producing vigorous intermittent fighting for 60-80 h.

Preliminary tests with etonitazene (ETZ), a benzimidazole derivative, has indicated a relatively weak potency in stimulating fighting in rats during withdrawal. However, ETZ can negate morphine withdrawal symptoms (Wikler et al, 1963) and is considered a highly potent analgesic (Collier et al, 1961). The present experiment was conducted to test the hypothesis that CNS stimulation during ETZ withdrawal would promote fighting.

Method. Twenty albino male rats about 100 days old and with average weight of 317 g were randomly assigned to five groups of four. Each group was placed in a single cage (18 x 18 x 25 cm) for 1 h on five occasions. Only three aggressive responses³ were noted over all control observations. Twelve animals were then placed on an increasing dosage schedule of ETZ individually administered in drinking water (for sustained intake and convenience). An original concentration of 10 mcg/ml was increased by 10 mcg/ml every 48 h to a maximum of 90 mcg/ml (duration of administration thus 18 days). Each animal was given 50 ml every 48 h and, when this was consumed, given tap water prior to the end of each 48 h period. In only rare instances did an animal fail to consume the ETZ solution available. The eight animals not on the ETZ schedule were also placed in individual cages with normal food and water available.

Five groups of four animals were then placed in group cages for 1 h four times daily at 6 h intervals. Group 1 was formed from four animals previously on ETZ and each animal received an IP injection of 2 mg/kg dextroamphetamine sulfate in sterile water prior to each grouping. Group 2 was also formed with ETZ treated animals each given IP injections of normal saline prior to each grouping. Group 3 was formed with ETZ treated animals given no injections prior to grouping. Groups 4 and 5 were formed from non ETZ treated animals with Group 4 receiving saline injections and Group 5 receiving 2 mg/kg dextroamphetamine sulfate injections.

Results. No fighting occurred in Groups 4 and 5. Groups 2 and 3 were highly comparable in extent and duration of fighting indicating no difference in fighting due to injection alone. The course of fighting for Group 2 is described in Fig. 1. (Group 3 is omitted from the figure since data points were nearly identical to that of Group 2.) Extent of fighting in Group 1 is apparent in Fig. 1. The nature of fighting in Group 1 was more vigorous than previously observed in other animals during morphine withdrawal. On days of peak fighting activity blood was noted on the walls and floor of the observation chamber and fighting postures included fighting on backs and sides as pictorially described for wild rats by Barnett (1963). Maximal fighting occurred on Days 5 and 6 post withdrawal, approximately the same interval prior to maximal fighting for morphine treated animals.

Duration of fighting behavior was 12 days for Group 1 and 10 days for Groups 2 and 3. On Day 7 two of the four daily observations were not made due to unavoidable circumstances and data points for Day 7 in Fig. 1 may be considered artificially depressed.

Discussion. Aggressive behavior in rats may be stimulated in a variety of additional ways usually entailing trauma to CNS tissues (lesions in the septum, hypothalamus, amygdala, pyriform lobe, or hippocampus) or

Fig. 1. Comparison of fighting behavior in two groups of rats after withdrawal from etonitazene administration. Dextroamphetamine and saline injections were given prior to each of four daily observation periods.

involving noxious stimuli such as electric shock to the feet. The present drug withdrawal method appears to lower threshold to irritating stimuli in the behavior of other rats in the immediate vicinity. A stimulant, such as amphetamine, may increase potential for aggressive behavior through stimulating activity and hence increasing irritation source as well as available energy drive for vigorous attack.

Also suggested in the present design is the influence of CNS stimulants upon organisms already under considerable distress. From the present results one would predict unusually aggressive behavior when amphetamines are taken under duress from another source.

Although the pharmacology of ETZ and morphine is not known well enough to specify locus of effect in the elicitation of withdrawal induced aggression, the method of induction appears reliable and further research may specify neurological detail. It is clear that in this case dextroamphetamine adds significant impetus to withdrawal induced aggression. Similar experimental approaches appear applicable for further experimental analyses in the psychopharmacology of aggressive behavior.

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NOTES

1. Now at Youngstown State University, Youngstown, Ohio 44507.
2. Now at E. R. Johnstone Training and Research Center, Bordenstown, N. J. 08505.
3. Although fighting behavior in rats is readily observable and has been described by a number of writers, no generally successful automatic recording device has been developed to our knowledge. We arbitrarily defined a fight as biting or striking movements with paws between two or more animals. Succeeding bouts were recorded following pauses in fighting for 2 sec or longer. Some aspects of definition and methodology have been recently presented (see H. Kaufman, *Psychol. Bull.*, 64, 351 (1966) and N. Azrin, *Psychology Today*, 1, 26 (1967)).
4. We thank Ciba Pharmaceuticals and Smith, Kline, and French Laboratories for kindly supplying the drugs used.