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BRIEF COMMUNICATION

Selective Antagonism of Isolation-Induced Aggression in Mice by Diazepam Following Chronic Administration

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MALICK, J. B. *Selective antagonism of isolation-induced aggression in mice by diazepam following chronic administration.* PHARMAC. BIOCHEM. BEHAV. 8(4) 497–499, 1978. – Benzodiazepines are non-selective (i.e., they only inhibit aggression at doses producing concurrent neuromuscular impairment) antagonists of isolation-induced aggression in mice following acute administration. However, in the present study diazepam was shown to be a selective antagonist of fighting in isolated mice following chronic administration for 5 days. When administered chronically, selective tolerance rapidly developed to the general CNS depression produced by diazepam whereas the antifighting activity was not diminished and, in fact, tended to be enhanced following multiple drug administrations. Thus, the antagonism of fighting in isolated mice by diazepam does not appear to be due solely to general CNS depressant properties.

Isolation-induced aggression Diazepam Chronic administration

IN GENERAL, benzodiazepines have been shown to inhibit many different types of aggression in animals [2, 3, 13, 14, 16, 19, 23, 25, 27]; however, in some cases this antagonism was non-selective in that it was only observed at doses that produced concurrent neuromuscular impairment. In contrast, under certain conditions, benzodiazepines have been reported to increase the frequency or intensity of some forms of aggressive behavior following either acute (single dose) [4,15] or chronic (multipledose) drug administration [8, 9, 12]. Benzodiazepines have also been reported to paradoxically increase aggression in man [6,10]. These differences in activities are not all that surprising when one considers the many different types of aggression which have different underlying physiological substrates [21].

It is generally accepted that benzodiazepines are non-selective (i.e., they suppress aggression only at doses that produce neuromuscular impairment) antagonists of isolation-induced aggression in mice [5, 17, 24, 25]; one exception is a study by Valzelli and coworkers [27] in which the benzodiazepines appeared to be selectively effective although no measure of neurotoxicity (e.g., rotarod, inclined-screen) was assessed in the same animals.

Studies have shown that the various actions of benzodiazepines follow different courses during chronic administration. The depressant action rapidly undergoes tolerance after a few doses [11] whereas the antianxiety activity fails to exhibit tolerance and may even increase with repeated doses [20].

The present study was designed to assess the effects of chronic administration of diazepam on fighting and neuromuscular coordination in isolated mice. The aim of the study was to answer the following: do benzodiazepines exert a selective antiaggressive activity in isolated mice or is the observed reduction in fighting following acute administration merely due to general CNS depression or ataxia?

METHOD

Isolation-induced aggression in mice was produced by a modification of the method of Yen and coworkers [29] and has been reported previously [1]. Briefly, CF No. 1–S male mice (18–22 g) were isolated for a period of 4 weeks and then tested for aggression by placing an isolated mouse into the home cage of another isolate. Pairs of mice were observed for 3 min, and presence or absence of fighting was recorded. Only mice that were consistent fighters were used for drug studies. Mice were retested for aggression 30 min after each drug administration. Each mouse in the drug-treated group (n = 40; 20 pairs of mice) received diazepam (10 mg/kg, IP) once a day at 10 a.m. for 5 econsecutive days. A control group (n = 20; 10 pairs) received vehicle IP on each test day and were tested under the same conditions. Immediately following the aggression test, the mice were checked for neurological impairment by gently placing them on a 45° inclined screen; any mouse that exhibited impaired performance was scored as being ataxic.

Diazepam was suspended in a 0.4% methylcellulose vehicle and administered IP in a volume of 10 ml/kg. The dose of diazepam used in this study was chosen since it was found to be the dose which would inhibit fighting in

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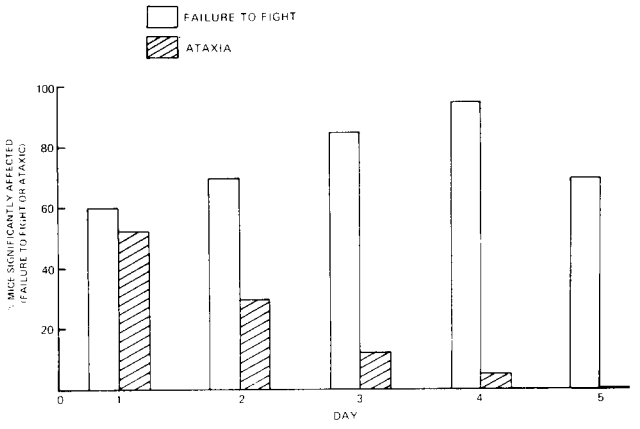

FIG. 1. Effects of chronic diazepam administration on aggression and neuromuscular coordination on an inclined screen in isolated mice. N = 20 pairs of mice.

approximately 50% of the mice tested in a previous study.

RESULTS

The results of this study are summarized on Fig. 1. Diazepam (10 mg/kg, IP) inhibited fighting in 60% of the mice tested and produced neuromuscular impairment (ataxia) in 52.5% of the animals on the first day of administration. Following daily administration of diazepam for 5 days, complete tolerance to the motor impairment occurred (see Fig. 1); in fact, diazepam only induced significant ($p<0.01$ compared to vehicle control; Fischer's Exact Probability; 7) ataxia on Days 1 and 2 of the study. In contrast, diazepam significantly inhibited ($p<0.01$; Fischer's Exact Probability; 7) aggression on all 5 days; thus, the antiaggressive activity of diazepam did not exhibit tolerance over the 5 day period and, with the exception of Day 5, the percent inhibition of fighting following diazepam tended to increase following multiple injections (see Fig. 1). The results with the vehicle-treated control group were not presented on Fig. 1 since none of the pairs of mice stopped fighting or exhibited neuromuscular impairment following vehicle throughout the 5 day period.

DISCUSSION

The finding that the general CNS depression (ataxia) produced by diazepam rapidly undergoes tolerance after repeated administration confirms the results of previous studies [11,20]. Since the antifighting activity of diazepam did not diminish over the same period, the inhibition of isolation-induced aggression following diazepam cannot be attributed to general CNS depression. Rather, diazepam appeared to exhibit a selective (i.e., antagonism of aggression without concurrent neuromuscular impairment) antiaggressive activity that was separable from the general depression upon chronic administration.

In previous studies, the antianxiety activity of another benzodiazepine, oxazepam, also failed to exhibit tolerance [20]. Also, the antiaggressive activity of chlordiazepoxide on footshock-induced fighting in rats did not exhibit tolerance [22]; however, in this study the authors failed to measure neuromuscular impairment in the same animals. However, in an isolation-induced timidity procedure [26], the antianxiety activity appeared to be reduced (although still statistically significant) following 8 days of chronic administration in mice.

Although the mechanism of action for the antiaggressive activity of the benzodiazepines is unknown, Wise and coworkers [28] have observed significant depression of both norepinephrine and serotonin turnover following acute oxazepam whereas only serotonin turnover was decreased following 6 daily doses of oxazepam. Thus, it is possible that a decrease in serotonin turnover is responsible for the antiaggressive activity of the benzodiazepines in isolation-induced aggression. Malick and Barnett [18] have demonstrated that serotonergic pathways are significantly involved in the regulation of isolation-induced aggression in mice.

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