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Facilitated Shock-Induced Aggression Following Antidepressive Medication in the Rat[1,2]

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EICHELMAN, B. AND J. BARCHAS. *Facilitated shock-induced aggression following antidepressive medication in the rat.* PHARMAC. BIOCHEM. BEHAV. 3(4) 601–604, 1975. – Rats were tested for changes in shock-induced fighting following treatment with antidepressants of both the dibenzazepine and monoamine oxidase inhibitor classes of drug. Rats were retested for shock-induced fighting 3, 4, and 5 days after initial injections of imipramine (10 mg/kg IP bid), amitriptyline (10 mg/kg IP bid), and desmethylimipramine (10 mg/kg IP bid), or saline. All three dibenzazepine groups showed increased levels of shock-induced fighting ($p<0.01$). In addition, rats were retested for shock-induced fighting 6, 30, 54, and 78 hours following the initiation of treatment with daily injections of saline, or the monoamine oxidase inhibitors: nialamide (100 mg/kg/day), iproniazid (150 mg/kg/day), and pargyline (20 mg/kg/day). All three monoamine oxidase inhibitor groups showed increased levels of shock-induced fighting after 30 hr ($p<0.001$). There was no difference in the jump threshold of rats treated with pargyline or saline.

Shock-induced aggression Rats Nialamide Iproniazid Pargyline Amitriptyline Imipramine Desmethylimipramine

DRUGS which alter mood states, particularly depression, have been linked through the catecholamine hypothesis of affective disease with altered catecholamine metabolism [15]. Central catecholamine metabolism appears clearly related to various forms of animal aggression [4]. In particular, drugs which appear to facilitate central adrenergic metabolism, such as rubidium, appear to facilitate irritable aggression in the rat [4, 7, 18]. One group of drugs which clearly alter catecholamine metabolism is the antidepressants, both dibenzazepine compounds [16] and monoamine oxidase inhibitors [17]. Drugs such as the dibenzazepines when used in repeated doses increase norepinephrine turnover [16]. Since with other conditions of increased catecholamine metabolism irritable aggression is increased [5, 7, 11], we posited that repeated administration of dibenzazepine compounds or MAO inhibitors could facilitate shock-induced aggression in the rat.

EXPERIMENT 1: DIBENZAZEPINES

Method

Animals. The animals were 60 male Sprague-Dawley rats (Hormone Assay, Chicago, Illinois) 240–260 g at the time of testing. The rats were housed separately with ad lib access to rat chow and water throughout the study.

Apparatus. The shock-induced fighting apparatus has been described previously [3]. Essentially it consisted of two Plexiglas boxes (32 X 25.5 X 30.5 cm) with stainless steel grid floors. Shock was delivered by a constant current source [2] at 2 mA for a duration of 0.5 sec every 7.5 sec.

Procedure. On the first day of the study the rats were randomly paired and ear-punched. For the first 3 days the rats were subjected to daily sessions of shock-induced fighting. These consisted of delivering 50 footshocks to each pair of rats and counting the number of attack responses made. Aggressive attacks were defined as a directed movement toward the opponent which resulted in contact, including at least one additional response of the following: biting, sparring, upright attack posturing, or supine submissive posturing, adopted by the attacked rat. These criteria have been successfully used previously [3]. For each day, an attack/shock percentage was calculated (the number of attacks divided by the number of shocks administered X 100). This daily percentage was then averaged over the 3 days to provide a baseline. The rat pairs were then divided randomly into 4 groups for treatment.

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The first group (n = 8 pr) received on Days 3 (after testing) through 8, injections of saline (1 cc, bid, IP). The second group (n = 8 pr) received imipramine (10 mg/kg, bid, IP), the third group (n = 7 pr) received amitriptyline (10 mg/kg, bid, IP), and the fourth group received desmethylimipramine (10 mg/kg, bid, IP) all in a schedule similar to the saline group. This dosage schedule and time course were chosen to closely follow the studies of others involving norepinephrine turnover [16]. The rat pairs were again tested for shock-induced fighting on Days 6 through 8 (after 3 to 5 days of drug). Again a three-day baseline of fighting was determined and compared with the predrug baseline by a matched-pairs t test, two tailed.

Imipramine, amitriptyline and desmethylimipramine were dissolved in saline.

Results

As indicated in Table 1, the saline injected group showed no significant change in shock-induced fighting. However, all three of the dibenzazepine-treated groups showed significant ($p<0.01$) increases in shock-induced fighting. This was reflected in an increase in the frequency of attack, rather than in the intensity.

EXPERIMENT 2: MONOAMINE OXIDASE INHIBITORS

A second group of antidepressant drugs, the monoamine oxidase inhibitors, is also posited to facilitate catecholamine metabolism [17] and consequently were tested to aid in the validation of the hypothesis that drugs which facilitate catecholamine metabolism facilitate shock-induced fighting. Secondly, this study attempted to determine whether there was any change in pain thresholds in the experimental group.

Method

Animals. The animals were 96 male Sprague-Dawley rats (Hormone Assay, Chicago, Illinois) 180–220 g at the time of testing. They were housed as in Experiment 1.

Apparatus. Identical to Experiment 1.

Procedure. With the first 64 rats, 4 groups of 8 pairs were randomly formed. The additional 32 rats were used in the second portion of the experiment. The initial 4 groups were tested for 3 daily test sessions identical to those described in Experiment 1. From this a baseline level of fighting was obtained for each group. The 4 groups then received daily IP injections of (1) saline; (2) nialamide, 100 mg/kg; (3) iproniazid, 150 mg/kg; and (4) pargyline, 20 mg/kg. These doses were chosen as representative doses at or above levels previously shown to inhibit MAO in the rat [1] and included both hydrazine (nialamide and iproniazid) and nonhydrazine (pargyline) MAOIs. The rats were again tested for shock-induced aggression 6, 30, 54, and 78 hr after the initial injections.

To demonstrate that any change in aggression was not due to a change in pain thresholds, the additional 32 rats were divided into 2 groups of 16 each. The control group was injected daily with saline (0.2cc, IP) and the experimental groups with pargyline (20 mg/kg, 0.2 cc, IP). Both groups were tested for jump thresholds 54 to 78 hr after the initial injections. The method for jump threshold measurement was modified from Lints and Harvey [12]. Briefly, 10 ascending and descending series (0.07, 0.1, 0.2, 0.3, 0.4, and 0.5 mA) of footshocks were given to the rats. The shock intensity at which each rat jumped 50% of the time was defined as the threshold value [3].

Iproniazid and pargyline were dissolved in saline. Nialamide was dissolved in acid and the pH adjusted to 3.5.

Results

Six hr after the initial injection, the nialamide group showed increased fighting from a baseline level of 17.6 percent to 32.5 percent ($p<0.001$, matched pairs t test, two tailed). All other groups remained unchanged. The attack percentages for the 3 subsequent test periods were then averaged for each group and compared with the predrug baseline averages. The saline control group remained unchanged, while all three MAO inhibitor groups showed markedly increased levels of fighting (see Table 2). Jump threshold measurements demonstrated the control rats to

TABLE 1

CHANGES IN ATTACK SCORE FOLLOWING CHRONIC DIBENZAZEPINE TREATMENT

		Predrug M		Postdrug M		
Group	N Pairs	Attacks per 50 Shocks	Percent	Attacks per 50 Shocks	Percent	Percent Difference in Attacks
Saline	8	10.2	20.4	8.9	17.8	− 2.6
Imipramine	8	9.4	18.8	16.9	33.9	+15.3*
Desmethylimipramine	7	7.8	14.7	14.9	29.9	+15.2†
Amitriptyline	7	4.2	8.5	14.5	29.1	+20.6‡

2-tailed matched pairs t test: *$p<0.01$ †$p<0.002$ ‡$p<0.001$

TABLE 2

CHANGES IN ATTACK SCORE FOLLOWING CHRONIC MAOI TREATMENT

Group	N Pairs	Predrug M		Postdrug M		Percent Difference in Attacks
		Attacks per 50 Shocks	Percent	Attacks per 50 Shocks	Percent	
Saline	7	8.8	17.5	9.0	18.0	+ 0.5
Iproniazid	8	12.1	24.2	25.3	50.6	+26.4*
Nialamide	8	8.8	17.6	25.2	50.4	+32.8*
Pargyline	8	9.0	17.9	20.4	40.8	+22.9*

*$p<0.001$, matched pairs 2-tailed t test

have a jump threshold of 0.26 ± 0.02 mA. The pargyline group threshold was 0.24 ± 0.02 mA, and not significantly different from the control threshold. These values are in agreement with previously reported thresholds for uninjected Sprague-Dawley rats [20].

DISCUSSION

These data appear to affirm the hypothesis that repeated doses of antidepressant drugs of both the dibenzazepine and MAOI classes facilitate shock-induced fighting in rats, in doses which do not necessarily alter jump thresholds. These findings extend the hypothesis that shock-induced fighting is closely correlated with a facilitation of a central adrenergic system which can be affected by stress [11], REM deprivation [5,13], rubidium [8,18] and perhaps selected CNS injury (e.g. 6-hydroxydopamine treatment [6]). The results of this study were obtained with repeated drug injections. They must be contrasted with acute, single dose studies where the converse may be true. Tedeschi *et al.* [19] reported a decrease in shock-induced aggression in mice following MAOIs and in general, Kumadaki *et al.* [10] found only a minimal effect on the aggressive behavior of bulbectomized rats with dibenzazepines. Similarly, paradoxical effects of imipramine have been shown biochemically by Schildkraut *et al.* [16] who report a decrease in the disappearance of intracisternally administered tritiated norepinephrine from rat brain following a single dose of imipramine, but an increased rate of disappearance during long-term administration. These time-dependent changes affecting a plastic nervous system [9] may be variables necessary to define and study in order to understand such paradoxical drug effects.

Lastly, the antidepressant drugs used in this study affect the central serotonergic system in ways similar to their effect on central adrenergic systems. However, manipulation of the serotonin system through depletion of brain serotonin with *p*-chlorophenylalanine or with the facilitation of serotonin turnover with cesium [14] does not alter shock-induced fighting in the rat [5,8]. This contrasts with the facilitation of norepinephrine turnover following rubidium treatment [7] and its concomitant increase in shock-induced aggression. Similarly contrasting, is the destructive effect of 6-hydroxydopamine on the central adrenergic system and this drug's concomitant alteration of shock-induced fighting [6]. This data supports the hypothesis that in the rat the effects of the antidepressants reported above are mediated through an adrenergic, rather than a serotonergic system.

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