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The Acute Effects of Antidepressant Drugs on the Performance of Conditioned Avoidance Behavior in Rats

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LUCKI, I. AND M. S. NOBLER. *The acute effects of antidepressant drugs on the performance of conditioned avoidance behavior in rats.* PHARMACOL BIOCHEM BEHAV 22(2) 261–264, 1985.—The effects of acute administration of 10 different antidepressant drugs were examined on the performance of a two-way conditioned avoidance response in rats. The antidepressant drugs impaired avoidance behavior by decreasing avoidance responding and increasing the number of escape failures. The order of effectiveness for increasing overall response latency at a common dose of 10 mg/kg was: desipramine, maprotiline, protriptyline, (+) oxaprotiline, nortriptyline, imipramine, amitriptyline, (−) oxaprotiline, fluoxetine, and chlorimipramine. Avoidance behavior was impaired most by those antidepressant drugs that are also potent inhibitors of norepinephrine uptake.

Antidepressant drugs Avoidance behavior Norepinephrine Rats

MANY reports have indicated that the acute administration of antidepressant drugs produces suppressive effects on conditioned behavior in animals. For example, the administration of imipramine or amitriptyline reduced response rates for food or water reward under various schedules of reinforcement in primates and in rats [8,9]. Acute treatment of rats with antidepressant drugs also retarded the acquisition of behavioral responses that would avoid the presentation of electric shock [6, 15, 17] as well as impaired the performance of avoidance responses that were learned prior to drug treatment [5,10].

These behavioral impairments in animals may provide models for studying the potential sedative, or behavior-impairing, effects of different antidepressant drugs in humans [7]. However, previous studies that showed impairments of conditioned behaviors by antidepressant drugs in rats have used just a few tricyclic compounds, such as imipramine or amitriptyline. The reason that antidepressant drugs produce such impairments on conditioned behaviors in animals is not known.

The tricyclic antidepressants produce a variety of pharmacological effects on brain monoaminergic neurons, but among their prominent effects is the inhibition of the reuptake of norepinephrine or serotonin [3,16]. Some tricyclic drugs such as desipramine are potent and relatively selective inhibitors of the reuptake of norepinephrine, while other tricyclics such as chlorimipramine are relatively selective inhibitors of the reuptake of serotonin. Some tricyclic antidepressants, such as amitriptyline and imipramine, are effective inhibitors of the reuptake of both monoamines [3, 13, 14]. Recently, a variety of nontricyclic antidepressant compounds have been developed with more selective actions on brain monoaminergic neurons. For example, maprotiline and (+) oxaprotiline are selective inhibitors of the reuptake of norepinephrine, whereas the isomer, (−) oxaprotiline, is relatively inactive [20]. In contrast, fluoxetine is a relatively selective inhibitor of the reuptake of serotonin [21].

The effects of such a wide variety of compounds with similar clinical antidepressant effects have not usually been studied systematically using a single conditioned behavior in animals. In the present study, we examined the ability of a series of 10 tricyclic and nontricyclic antidepressant drugs for their ability to produce impairment in the performance of a shuttle box conditioned avoidance response (CAR) by rats.

METHOD

Subjects

The subjects were 14 male albino Sprague-Dawley rats (Ace Animals, Boyertown, PA) that weighed 250–300 g at the start of the experiment. The animals were housed in groups of four with free access to food and water in an animal colony on an alternating 12-hour light-dark cycle.

Procedure

Two automated shuttle cages (BRS/LVE Corp., Beltsville, MD) that were enclosed by ventilated sound-attenuating chambers were used in these experiments. Each chamber was divided into two compartments (19×25×19

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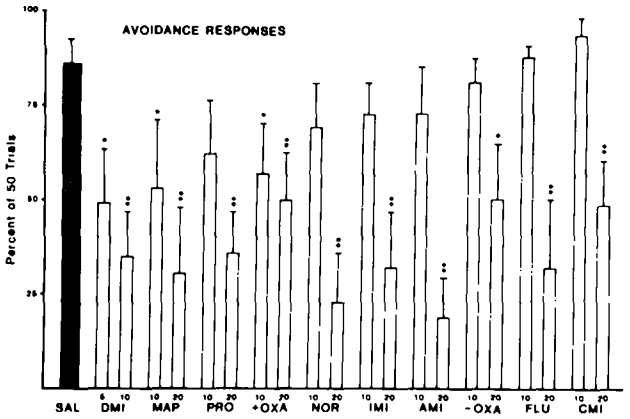

FIG. 1. The effects of acute administration of antidepressant drugs on avoidance responding during performance of the conditioned avoidance response. The bars represent the mean percentage of trials when an avoidance response (latency <5 sec) was measured, with the brackets indicating 1 SEM. The abbreviations represent: SAL, saline; DMI, desipramine; MAP, maprotiline; PRO, protriptyline; +OXA, (+) oxaprotiline; NOR, nortriptyline; IMI, imipramine; AMI, amitriptyline; −OXA, (−) oxaprotiline; FLU, fluoxetine; and CMI, chlorimipramine. *Indicates the value differed significantly from corresponding values obtained after the administration of 0.9% NaCl according to Student's t-test, $p<0.05$; **$p<0.01$.

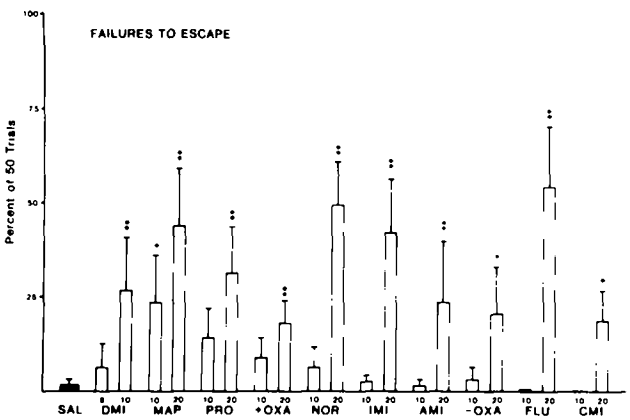

FIG. 2. The effects of acute administration of antidepressant drug on escape failures during the performance of the conditioned avoidance response. The bars represent the mean percentage of trials that failed to measure any response during the 15-sec trial, with the brackets indicating 1 SEM. The abbreviations and statistics are given in the caption for Fig. 1.

cm) by a 4-cm high aluminum barrier. The grid floor of the chamber tilted when the rat traveled across the barrier to the other compartment thereby closing a microswitch that allowed the monitoring of the position of the rat in the chamber at all times. A 2000-Hz tone was delivered through a single Sonalert device attached to the top of each chamber midway between compartments. Scrambled shock was delivered to the grid floor by two shock generators (BRS/LVE Model SGS-004). Stimulus presentation and recording of the responses were programmed with a Franklin Ace 1000 microcomputer (Franklin Computer Corp., Pennsauken, NJ) controlling a solid-state interface (MED Associates, East Fairfield, VT).

A tone of 92 dB served as the conditioned stimulus (CS) and an electric shock of 0.8 mA was the unconditioned stimulus (US). On each trial, the presentation of shock could be prevented if the animal jumped over the barrier within 5 sec of presentation of the tone (CS). The response was then classified as an avoidance response. After 5 sec, the shock (US) was presented along with the tone (CS) for 10 sec. If a response was not made within 15 sec of the onset of the presentation of the tone (CS), both stimuli were terminated, the trial was ended, and the response was scored as an escape failure. Crosses of the barrier that occurred in the absence of either stimulus were recorded as intertrial crosses. An average intertrial interval of 50 sec (range=40–60 sec) was used.

Animals were initially trained to perform the CAR on a 200-trial acquisition session. Thereafter, experimental sessions were conducted twice each week consisting of the presentation of 50 avoidance trials. Each session began with a 10-min period when the animals were acclimated to the chamber. Before exposure to drugs, the animals were trained until they each reached an average performance criterion of 80% avoidance responses on two consecutive sessions. Two or three drug-free sessions were always conducted between the consecutive administration of drugs. Sessions involving drug injections were always spaced at least one week apart. All drugs were administered by intraperitoneal injection one hour prior to testing.

Drugs

Desipramine, imipramine, chlorimipramine, fluoxetine, amitriptyline, protriptyline, (+) and (−) oxaprotiline (all hydrochloride salts) were dissolved in deionized water. Maprotiline hydrochloride was wet with Tween 80, diluted with deionized water, and injected as a suspension. Administration of the Tween 80 vehicle alone did not produce significant alterations in avoidance behavior. Drug doses are expressed as the free base.

RESULTS

The antidepressant drugs showed a range of ability to impair performance of the conditioned avoidance response. Changes in avoidance responding are presented in Fig. 1 and changes in the escape failures are presented in Fig. 2. Desipramine was the most potent of the antidepressant drugs that were examined. At 5 mg/kg, desipramine significantly reduced the percentage of avoidance responses without impairing the ability of the animals to escape from shock, when compared with performance following the administration of saline. Although 10 mg/kg of desipramine also reduced avoidance responding, escape failures were increased significantly by this dose of desipramine. Maprotiline and (+) oxaprotiline reduced avoidance responding significantly at 10 mg/kg, although both drugs increased the number of escape failures at this dose as well. The other antidepressant drugs did not affect avoidance responding significantly at 10 mg/kg. Each of the antidepressant drugs tested at 20 mg/kg reduced avoidance responding significantly, while escape

TABLE 1

AVERAGE OVERALL LATENCIES FOR RESPONDING OF AVOIDANCE BEHAVIOR FOLLOWING THE ADMINISTRATION OF ANTIDEPRESSANT DRUGS*

Treatment			Latency	N
Saline			3.17 ± 0.40	13
	5 mg/kg	N	10 mg/kg	N
Desipramine	5.40 ± 1.00†	7	9.70 ± 1.17†	7
	10 mg/kg	N	20 mg/kg	N
Maprotiline	6.73 ± 1.69†	7	9.73 ± 1.86†	7
Protriptyline	6.05 ± 1.42†	7	8.35 ± 1.52†	7
(+) Oxaprotiline	5.60 ± 1.04†	7	6.70 ± 1.18†	7
Nortriptyline	4.83 ± 1.00	7	10.11 ± 1.47†	7
Imipramine	4.08 ± 0.35	7	9.23 ± 1.70†	7
Amitriptyline	3.81 ± 0.64	7	8.90 ± 1.21†	6
(−) Oxaprotiline	3.70 ± 0.49	6	7.18 ± 1.63†	6
Fluoxetine	3.41 ± 0.33	6	10.31 ± 2.15†	6
Chlorimipramine	2.49 ± 0.31	6	6.66 ± 1.10†	6

*The values represent the average latency (sec) to respond on all 50 trials of the CAR session, ±1 SEM.

†Indicates the value differs significantly than values obtained following the administration of saline according to Student's t-test, $p<0.05$.

TABLE 2

AVERAGE INTERTRIAL CROSSES DURING PERFORMANCE OF THE CONDITIONED AVOIDANCE RESPONSE AFTER ANTIDEPRESSANT DRUGS*

Treatment			Intertrial Crosses	N
Saline			19.0 ± 3.6	13
	5 mg/kg	N	20 mg/kg	N
Desipramine	7.7 ± 3.0†	7	4.9 ± 1.3†	7
	10 mg/kg	N	20 mg/kg	N
Maprotiline	6.9 ± 1.1†	7	4.3 ± 1.1†	7
Protriptyline	6.3 ± 2.5†	7	5.0 ± 1.7†	7
(+) Oxaprotiline	2.4 ± 0.6†	7	4.0 ± 1.4†	7
Nortriptyline	5.4 ± 0.9†	7	7.6 ± 1.4†	7
Imipramine	3.4 ± 0.8†	7	8.6 ± 4.1†	7
Amitriptyline	12.4 ± 3.3	7	8.5 ± 2.6†	6
(−) Oxaprotiline	13.2 ± 3.2	6	12.5 ± 2.5	6
Fluoxetine	8.2 ± 1.6†	6	3.7 ± 1.7†	6
Chlorimipramine	17.3 ± 5.0	6	7.2 ± 1.7†	6

*The values represent the number of intertrial crosses per 50-trial session, ±1 SEM.

†Indicates the value is significantly lower than values obtained following the administration of saline according to Student's t-test, $p<0.05$.

failures increased significantly at this dose when compared to the administration of saline.

The average response latency for all 50 trials is shown in Table 1 as a means of comparing the relative overall effects of the 10 antidepressant drugs. Desipramine was the most potent antidepressant drug at producing increases in response latency. Maprotiline, protriptyline, and (+) oxaprotiline caused significant increases in response latency at 10 and 20 mg/kg. The other antidepressant drugs examined increased response latency significantly only at 20 mg/kg.

Although the intertrial crosses measured during CAR performance (Table 2) also tended to be reduced when overall response latencies were increased, this did not occur in all cases. For example, 10 mg/kg nortriptyline, imipramine, and fluoxetine produced significant reductions in intertrial crosses when overall performance on the CAR was not significantly affected by this dose. Nearly all of the antidepressant drugs produced significant reductions in intertrial crosses at 20 mg/kg. However, (−) oxaprotiline did not cause a significant reduction in intertrial crosses at 20 mg/kg even though CAR performance was significantly impaired by this dose.

DISCUSSION

A variety of antidepressant drugs were examined for their ability to impair performance of the conditioned avoidance response in rats. Desipramine was the most potent of the antidepressant drugs examined. At 5 mg/kg, desipramine produced a selective impairment of avoidance responding, since the ability to escape from shock was not affected by this dose. This pattern of behavior on the CAR is similar to that produced by neuroleptic drugs such as chlorpromazine [19]. Desipramine was followed in potency by maprotiline, (+) oxaprotiline, and protriptyline which decreased avoidance responding and increased overall response latency significantly above control values at 10 mg/kg. However, these drugs differed from the pattern of behavioral impairment on the CAR caused by desipramine because escape failures were also increased significantly. The remaining drugs produced significant impairments in avoidance responding and increased escape failures at the highest dose tested, 20 mg/kg.

The impairment in CAR performance was usually accompanied by a significant reduction in intertrial crosses. However, for some drugs, intertrial cross behavior was significantly reduced at doses that did not impair CAR performance significantly. Thus, adjunctive or exploratory behaviors in the chamber between trials may be more sensitive to impairment by these antidepressant drugs than the conditioned behavior. It is also interesting that the highest dose of (−) oxaprotiline (20 mg/kg) produced a significant reduction in CAR performance without reducing the accompanied intertrial cross behavior. In contrast, the isomer (+) oxaprotiline produced significant reductions in both intertrial crosses and avoidance behavior at the lower dose tested (10 mg/kg). These behavioral differences between the isomers may be related to their different pharmacological effects on noradrenergic neurons [20]. The differences in drug effects on intertrial crosses and avoidance behavior suggests that the impairment of CAR performance by antidepressant drugs may represent more than a simple ordering of their relative incapacitating effects on motor behaviors. However, the behavioral mechanisms that underlie these actions of antidepressant drugs, and their relationship with how neuroleptic drugs impair CAR performance, remain to be examined.

The acute administration of antidepressant drugs would be expected to produce a variety of effects on monoaminergic neurotransmission in the central nervous system [16]. Prominent among these effects is the ability of antidepressant drugs to inhibit the reuptake of norepinephrine or serotonin [3, 13, 14]. It is interesting that the four antidepressant drugs that were most potent at reducing

overall response latency on the CAR, desipramine, maprotiline, protriptyline, and (+) oxaprotiline, are all considered potent and selective inhibitors of the reuptake of norepinephrine [3, 13, 14, 20]. However, no direct evidence for the involvement of norepinephrine neurons in these behavioral effects is currently available. Moreover, all of the other antidepressant drugs were effective at impairing CAR performance at 20 mg/kg, and some of these drugs (e.g., fluoxetine and (−) oxaprotiline) would not be expected to inhibit the reuptake of norepinephrine at even this high dose. This would suggest that other pharmacological effects of these drugs are also involved in their effects on CAR performance. Among other pharmacological effects, the antidepressant drugs show affinity for alpha-noradrenergic, serotonin, histamine, as well as muscarinic cholinergic receptors [4,11]. However, the order of potency for antidepressant drugs to produce these effects *in vitro* was not related to their ability to impair CAR performance in the present experiment.

Some antidepressant drugs, such as amitriptyline or imipramine, are especially effective at producing sedative effects and behavioral impairments in humans [1,2]. These sedative effects, however, would not appear to be related to the relative ability of antidepressant drugs to disrupt avoidance behavior in rats. In particular, while desipramine was the most effective antidepressant drug that impaired avoidance behavior in rats, desipramine is also known to be a relatively nonsedating antidepressant drug in humans [2]. Unfortunately, the sedating effects of the other antidepressants used in this study have not been studied as extensively in humans. The sedative side effects of antidepressant drugs has been suggested to be associated with their ability to block alpha-adrenergic or histamine receptors [12,18], and desipramine has a relatively poor affinity for each of these receptors.

The kinds of information provided by the present experiment will probably be most useful to investigations that attempt to study the common behavioral effects of the diverse variety of antidepressant drugs that are currently available. The behavioral reasons that antidepressant drugs impair CAR performance and the neuropharmacological mechanisms that might underlie these effects remain to be explored.

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