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PHARMACOLOGICAL CONTROL OF AGGRESSIVE BEHAVIOR IN MICE

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The test of aggressiveness in mice caused by prolonged isolation was employed to evaluate the possible anti-aggressive activity of a number of centrally active drugs. A score to evaluate the intensity of aggressive behavior is described.

Aggressiveness
Antidepressant
MAO inhibitor
Tranquilizers
Neuroleptics
Barbiturates
Stimulants
Psychotomimetics
Autonomic system

It is well known from the observations of Allee (1942), Scott (1947) and Yen, Stanger and Millman (1959) that certain strains of mice (Valzelli, 1967; Valzelli and Garattini, 1967) submitted to prolonged isolation develop aggressive behavior which becomes evident when mice are again caged together with 2, 3 or 4 mice per cage. This test was used in standard conditions, as described below, to evaluate the possible anti-aggressive activity of a number of drugs belonging to different pharmacological classes.

Male Swiss albino mice, weighing about 20 ± 2 g were isolated in Makrolon cages (internal size 21 × 15 × 13 cm) for 4 weeks at a room temperature of 22°C and 60% relative humidity and fed a normal balanced diet *ad libitum*. To test the aggressive behavior the animals were grouped in threes and their aggressiveness was evaluated at different times after intraperitoneal saline or drug treatment. The mice were kept together for 5 min. The score used to evaluate the degree of aggressiveness (Valzelli, 1966) was as follows:

0 = The animals show no interest in their test partners, except occasional nosing.
25 = Frequent vigorous nosing and tail rattling. The animals assume a fighting position and occasionally attack the test partners (no more than 3-4 times in the period of 5 min).
50 = Tail rattling, squeaking, powerful attacks (no more than 10 times in the period of 5 min).
75 = The animals follow their partners, attacking and biting for most of the time.
100 = The attacks cover practically the entire period of observation.

The reproducibility of the results was frequently checked by independent observers on a blind basis. At the end of the period of isolation, the animals were invariably aggressive in 100% of the cases with a score of 100. Saline or solvents used, as shown in table 1, did not affect the aggressive behavior.

Table 1 shows the effect of a number of drugs grouped according to their principal pharmacological activity. Results are expressed as percent inhibition in relation to controls. The aggressive behavior was usually tested at 0.5, 1, 2, 4, 6, 8 and 24 hr after the administration of the drug. This procedure did not decrease the degree of aggressiveness in untreated animals. The drug was given to all the three animals involved in the test. A minimum of 6 mice was used for each dose of drug. Mice were treated only once.

It is evident from the table that many drugs were able to reduce the aggressive behavior of isolated mice. Among the drugs able to block the aggressive behavior completely are amitriptyline, meprobamate, tybamate, chlordiazepoxide and its derivatives, phenothiazines, reserpine, hexobarbital, ampyzine and yohimbine. It is interesting that amitriptyline differed from

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Table 1
Effect of several drugs on mice made aggressive by prolonged isolation.

Treatment	ml or mg/kg i.p.	% Inhibition of aggressive behavior min	max	Duration of the inhibition (hr)
Solvents				
Saline				
Arabic gum 4%	1	0	0	0
Arabic gum 20%	1	0	0	0
Tween 80 2%	1	0	0	0
Drugs				
Antidepressant				
Amitriptyline	10	75	100	1
	20	25	100	3
	30	25	100	6
Imipramine	10	0	0	0
	20	25	25	0.5
Desipramine	20	0	0	0
MAO inhibitors				
Phenelzine	20	0	0	0
Pheniprazine	5	25	50	7
	10	25	50	2
Tranylcypromine	5	25	50	32
	10	25	50	32
	15	25	50	32
Tranquilizers				
Meprobamate	10	25	25	1
	20	25	75	2
	40*	75	100	2
Tybamate	10	50	75	4
	20	50	75	6
	40	75	100	6
Trioxazine	50	25	50	1
	75	25	75	6
Chlordiazepoxide	7.5	25	100	2
	10	50	100	7
	30*	100	100	2
Diazepam	7.5	25	100	2
	15	50	75	2
	20	50	100	6
Oxazepam	10	25	75	6
	15	75	100	6
Nitrazepam	7.5	25	100	4
	15	25	100	4
	30*	75	100	6
Neuroleptics				
Chlorpromazine	2.5	25	100	6
	10*	75	100	8
Levomepromazine	0.3	25	100	24
	0.6	25	100	36
	1.2	25	100	48
Propericiazine	0.5	25	100	2
	1.0	75	100	6
Reserpine	0.6	50	100	7
	1.2*	75	100	48
Barbiturates				
Hexobarbital	5	75	100	4
Phenobarbital	5	25	75	4
Pentobarbital	5	25	25	2

Table 1 (cont.)

Treatment	ml or mg/kg i.p.	% Inhibition of aggressive behavior min	max	Duration of the inhibition (hr)
Stimulants				
Amphetamine	5	0	0	0
Magnesium pemoline	100	0	0	0
Methylphenidate	5	25	50	7
	10	25	25	4
Psychotomimetics				
Lysergic acid diethylamide	0.2	0	0	0
Mescaline	5	0	0	0
Hybogaine	20	50	50	2
Inhibitors of the autonomic system				
Atropine	2	25	75	6
Methysergide	0.4	0	0	0
Propranolol	20	50	75	2
Phentolamine	10	25	50	8
Miscellaneous				
Ampyzine	25	25	75	32
	50	25	75	96
	100	50	100	96
Opipramol	10	25	25	1
	20	25	75	4
γ-aminobutyric acid	250	0	0	0
Yohimbine	4	25	75	4
	8	25	100	6
	16	75	100	6
Probenecid	100	0	0	0
	200	25	75	4

* Signs of overt neuromuscular impairment.

"min" and "max": represent the minimal and maximal inhibition observed during the period of the reduced aggressiveness.

other tricyclic antidepressant agents. This is probably related to the fact that amitriptyline is more neuroleptic than other congeners. For tranquilizers, neuroleptics and barbiturates it is difficult to decide how much the observed effect was associated with the expected depression of the CNS. Further studies will be necessary to clarify this point. In some cases neuromuscular impairment was evident and explained the reduction of the aggressive behavior.

Surprisingly some psychomimetics, reported to induce aggressiveness in normal animals, such as LSD and mescaline (Haley, 1957) showed an inhibitory effect in this test. According to Melander (1960) an explanation may be that the oriented aggressive behavior was impaired because of the superimposed excitatory activity of the drugs.

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