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Differential Activity of Some Psychotropic Drugs as a Function of Emotional Level in Animals

L. VALZELLI and S. BERNASCONI

Istituto di Ricerche Farmacologiche "Mario Negri",
Via Eritrea 62, I-20157 Milano, Italy

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Abstract. The activity of various psychotropic drugs was tested on the abnormal behavior induced by prolonged isolation in both mice and in rats. It is suggested that the different effects shown by the drugs on the various behavioral profiles of the two species considered are dependent on the emotional level of the experimental animals.

Key-Words: Isolation in Rat — Emotional Level — Psychotropic Drugs — Isolation in Mice — Abnormal Behavior.

It is well known that prolonged isolation from the normal social environment is able to induce severe behavioral abnormalities in mice as well as in rats (Allee, 1942; Goldberg and Salama, 1969; Salama and Goldberg, 1970; Scott, 1947; Seward, 1946; Valzelli, 1967, 1969a; Yen *et al.*, 1959). In particular, isolated male mice develop a strong inter-specific aggressive behavior which becomes evident when two or three isolated individuals are put in contact in the same cage (Valzelli, 1967, 1969a).

Prolonged isolation in rats produces three different types of abnormal behavior which were tentatively defined as "friendly", "indifferent" and "muricide" toward a mouse put into the cage (Valzelli, 1970), according to the analysis of a number of behavioral patterns shown toward the intruder (Valzelli and Garattini, 1971).

The intraspecific aggressiveness in rats, defined as muricide, has previously been described and it can be induced by brain surgery (Karli, 1956; Karli and Vergnes, 1963; Vergnes and Karli, 1963), by genetic selection (Horovitz *et al.*, 1965, 1966) or, as mentioned above, by prolonged isolation (Goldberg and Salama, 1969; Salama and Goldberg, 1970; Sofia, 1969; Valzelli, 1970). The so-called friendly and indifferent behavior, arising from this last experimental situation, has not been described before.

This communication reports the effect of a number of psychotropic drugs on the different expression of altered behavior shown by mice and rats submitted to isolation.

Materials and Methods

Male Swiss Albino mice, weighing about 20 ± 2 g, were isolated in single Makrolon cages (internal size = $21 \times 15 \times 13$ cm) for 4 weeks at a constant room temperature of 22°C and 60% relative humidity and fed ad libitum. To test the aggressive behavior, the animals were grouped in threes and their aggressiveness was evaluated at different times after intraperitoneal administration of saline or drug. The degree of aggressiveness was scored as reported elsewhere (Valzelli, 1967; Valzelli *et al.*, 1967).

The reproducibility of the results was checked on a blind basis. At the end of the period of isolation, the animals were constantly aggressive in 100% of the cases, with a score of 100.

Wistar male rats, weighing 200 ± 10 g, were isolated in single Makrolon cages (internal size = $14 \times 24 \times 41$ cm) for a period of 6 weeks, at a constant room temperature of 22°C and 60% relative humidity and fed ad libitum. The development of the different behavioral profiles was followed during the entire period of isolation, by putting a naive normal mouse in contact with the isolated rat and evaluating the muricide, friendly or indifferent behavior according to the score shown in Table 1.

Table 1. Different types of behavior shown by rats submitted to 6 weeks isolation toward a mouse put into their cage (*N* = normal, *M* = muricide, *F* = friendly and *I* = indifferent rats) expressed as percent of animals presenting the characteristics listed below

Behavioral ^a patterns	Types of animals			
	<i>N</i>	<i>M</i>	<i>F</i>	<i>I</i>
Approaching	100	100	100	4
Sniffing	100	20	100	4
Licking	56	0	100	0
Grooming	15	0	64	0
Nest preparing	0	0	22	0
Picking up	0	0	91	0
Carrying around	0	0	87	0
Joking	18	0	65	0
Jumping	0	10	12	0
Incoordinated hyperactivity	0	0	34	0
Tremor	0	0	12	0
Piloerection	2	100	0	0
Digging	0	85	0	0
Compulsive eating and drinking	0	16	2	67
Attacking	0	100	0	0
Killing	0	100	0	0

^a Observations made by two observers in 800 rats.

The muricide reaction, by which the rat kills the mouse by breaking its neck, was obtained in our experimental conditions within $10 \text{ min} \pm 3$. The term "indifferent" was adopted to indicate a complete lack of interest by the rat for the presence of a mouse in the cage. This behavior is quite different from the normal one for rats not submitted to isolation. The so-called "indifferent" behavior might be considered as an expression of a deep emotional blockade, preventing the development of any oriented behavior toward the intruder animal put into the cage.

The behavior of those rats defined as "friendly", for lack of a more adequate definition, is more complex. They exhibit an active behavior toward the mouse, reminiscent of animals playing among themselves with some inclination to nurse, e.g. the preparation of a nest in which they put the mouse.

Isolation produces approximately 30% of "muricide" rats, with 25% of "friendly" and 45% of "indifferent" animals (Valzelli and Garattini, 1971).

All the drugs employed were administered intraperitoneally both in isolated mice and rats, and the effect was followed for a period of 48 h: as reported elsewhere for aggressive mice (Valzelli *et al.*, 1967), saline or other solvents employed did not affect the different behavioral patterns (Table 2).

Results and Discussion

In Table 2 the effect of a number of drugs upon the behavior of isolated mice and rats is shown. The data obtained indicate that benzodiazepines are effective in blocking the aggressive reaction in mice but they are unable to modify the muricide activity in rats, while tricyclic antidepressants such as imipramine and desipramine, block the muricide response completely and for a long time, as shown by Horovitz (1965) and Horovitz *et al.* (1966), but without affecting the aggressiveness in mice, as reported earlier by Valzelli *et al.* (1967).

Neuroleptic drugs block both the aggressiveness in mice and the muricide behavior in rats. In particular, the butyrophenones induce friendly rats to become indifferent, as some stimulant derivatives do. Moreover, yohimbine blocks both aggressiveness in mice, as previously reported (Valzelli *et al.*, 1967) and muricide behavior in rats. This drug is also able to transform the friendly rats into indifferent ones. Fenfluramine and methylphenidate, decreased aggressive behavior in mice whereas amphetamine and fencanfamine did not. However, all four drugs inhibited the muricide activity of isolated rats.

Some apparent discrepancies in the antiaggressive properties of chlordiazepoxide and other drugs in mice and rats, compared with the activity on rotarod performance of the animals reported by others

Table 2. Activity of some psychoactive drugs on different types of behavior by prolonged isolation in mice (aggressive mice = A) and in rats (M = muricide, F = friendly and I = indifferent rats)

Treatment	ml or mg/kg i.p.	% inhibitory effect on			
		A	M	F	I
Saline	1	0	0	0	0
Tween 80 2%	1	0	0	0	0
Carboxymethylcellulose 0.5%	1	0	0	0	0
Chlordiazepoxide	5	100 (2)	0	0	0
Diazepam	10	100 (2)	0	0	0
Medazepam	10	100 (1½)	0	0	0
	25	100 (3)	0	0	0
Oxazepam	15	100 (6)	0	0	0
Imipramine	10	0	100 (15)	0	0
Desipramine	10	0	100 (36)	0	0
Chlorpromazine	5	100 (7)	100 (7)	0	0
Propiclidazine	1	100 (6)	100 (7½)	0	0
Haloperidol	1	75 (5)	100 (3½)	100* (6)	0
Triperidol	1	100 (6)	100 (10)	100* (12)	0
Amphetamine	5	0	100 (20)	0	0
Fencanfamine	20	0	100 (8)	80* (4)	0
Fenfluramine	15	50 (2)	100 (5½)	100* (2)	0
Methylphenidate	10	50 (5)	100 (6)	100* (2)	0
Lysergic acid diethylamide	0.2	0	0	100* (2)	0
Yohimbine	10	100 (6)	100 (1½)	100* (4)	0

* The animals become "indifferent".

Each figure corresponds to ten animals. The duration of the observed effect in hours is in brackets.

(Sofia, 1969), can be accounted for by differences in the strains of animals employed. These differences may also be explained by the much higher doses used when studying locomotor activity than those used in the investigation of aggressive behavior (Christmas and Maxwell, 1970).

It is difficult at present to interpret the different sensitivities of the two experimental models of abnormal behavior induced by prolonged isolation as far as drug action is concerned. Two main factors should be considered in this respect.

Firstly, some nonspecific pharmacological activities, such as muscle relaxation by benzodiazepines or stimulation by amphetamine-like agents may reach a different intensity on the two animal species considered and they may therefore influence the final response observed in terms of behavior.

Secondly, the differences observed might reflect differences in drug metabolism between the species and thus in the behavioral patterns

produced. It should be mentioned that diazepam is transformed into N-demethyldiazepam and oxazepam in mice but not in rats (Marcucci *et al.*, 1968a, b); imipramine disappears more rapidly in mice than in rats (Dingell *et al.*, 1964) while amphetamine is hydroxylated on the phenyl ring in rats (Dring *et al.*, 1966) but not in mice (Dolfini *et al.*, 1969). Furthermore, the sensitivity to amphetamine and fencanfamine is increased in isolated versus normal mice (Consolo *et al.*, 1965a, b).

Despite this criticism, it is suggested that psychotropic drugs can exert a different effect in relation to the emotional level of the experimental animals (Valzelli, 1969b, 1971), as has also recently been reported in man (McNair *et al.*, 1970).

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Prof. Luigi Valzelli
Istituto di Ricerche Farmacologiche "Mario Negri"
Via Eritrea 62
I-20157 Milano, Italia

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