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EFFECTS OF DRUGS ON BEHAVIOUR OF AGGRESSIVE MICE

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1 The occurrence of 11 aggressive and non-aggressive activities was observed in aggressive male mice treated with drugs in paired interactions with non-aggressive males given water. Effects of chlordiazepoxide, diazepam, barbitone, chlorpromazine, imipramine, (+)-amphetamine, lysergic acid diethylamide (LSD) all given orally and of intraperitoneal scopolamine were investigated.

2 Scopolamine (0.25 and 0.75 mg/kg), (+)-amphetamine (0.25 and 1 mg/kg), chlorpromazine (2.5 mg/kg), diazepam (10 mg/kg) and chlordiazepoxide (50 mg/kg) reduced aggressive activities (attacks, aggressive unrest) without inhibiting walking across the cage or rearing in the aggressive mice. Thus, the inhibition of aggression induced by these drugs does not seem to be due to neuromuscular impairment and seems to this extent specific. On the other hand, imipramine lessened aggressive activities only at a dose (80 mg/kg) which also decreased walking across the cage and rearing. Barbitone or LSD did not change aggression at either dose tested (20 and 60 or 0.01 and 1 mg/kg, respectively). Aggressive activities were increased significantly only by chlordiazepoxide at a dose of 5 mg/kg.

3 (+)-Amphetamine (0.25 mg/kg) and scopolamine (0.75 mg/kg) increased escapes and alert postures, respectively, in the aggressive mice.

4 Diazepam and chlordiazepoxide decreased tail rattling at 1 and 5 mg/kg, respectively, doses 10 times lower than those inhibiting attacks. The other drugs tested inhibited tail rattling only at doses reducing attacks. Tail rattling appears to be a convenient measure for testing effects of drugs on behavioural conflict.

5 Diazepam (5 and 10 mg/kg), chlordiazepoxide (20 and 50 mg/kg), barbitone (60 mg/kg) and scopolamine (0.25 and 0.75 mg/kg) increased sociable activities (sniffing, following partners and climbing over them) whereas (+)-amphetamine, chlorpromazine, imipramine and LSD did not. Effects of the drugs on sociable activities in aggressive mice seem to correlate with their action on punished responding and other types of suppressed behaviour.

Introduction

When male mice are isolated for 3 to 5 weeks and are then introduced singly to a non-aggressive group-housed male in a neutral cage, their behaviour can be predominantly aggressive, predominantly timid, or predominantly sociable. Kršiak (1975) described the effects of certain drugs on the mainly timid mice. The present paper describes drug effects on the aggressive animals.

The first aim of the present study was to try to assess the relative specificity of action of some psychotropic drugs on aggressive behaviour occurring between strange male mice, which is still unclear in spite of voluminous research literature on the subject (Miczek & Kršiak, 1978). Selectivity of behavioural effects of drugs was assessed by comparing changes of acts and postures involving a similar type of movement but occurring in another behavioural context in the same animals. Though this procedure seems to provide a more relevant measure of selectivity of drug effects on agonistic behaviour than some conventionally used indices of neuromuscular impairment (e.g. the rota-rod test, Kršiak, 1975), it has been followed only rarely in testing effects of drugs on intraspecies aggression in mice. To avoid the problem of confounding effects produced by administration of drugs to the test animal with those exerted by interaction with drug-treated partners, which hampers evaluation of many published data on drug action on aggressive behaviour in mice (Miczek & Kršiak, 1978), drugs were always given only to one member of each pair, i.e. to the aggressive isolate.

Most published pharmacological studies have been focused exclusively on attacks between mice, ignoring effects of drugs on other behavioural activities occurring in aggressive mice. Therefore, the second aim of the present study was to ascertain the value of non-aggressive behavioural activities for assessment of the behavioural activity of drugs.

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Methods

Subjects, housing and apparatus

Male albino random-bred Swiss mice weighing 18 to 20 g at the beginning of the experimental housing were used. They were housed singly or in groups of 20. The cages used for the individual housing had solid metal walls 13 cm high with wire-mesh floors (8 × 16 cm). The isolates were only handled on experimental days. The mice kept in groups were housed in standard plastic cages 25 cm high with solid bottoms (22 × 38 cm) covered with wood shavings. All mice were housed in a natural day-and-night cycle at temperatures ranging from 22 to 24°C. Food and water were available permanently *ad libitum*.

The mice were observed in transparent cages (20 × 30 × 20 cm) with wood shavings on the floor and open tops. The observations were performed in a quiet experimental room from 08 h 30 min to 16 h 00 min under moderate artificial dispersed lighting.

Procedure

Social interactions were started after 3 to 5 weeks of isolation, always involving one singly-housed and one group-housed mouse in the observation cages. The isolates were allowed 30 min adaptation in the observation cages before the group-housed partners were introduced; interactions ended after 4 min. This procedure, which suppresses aggression in group-housed mice and reduces their social behaviour, facilitates exhibition of active social behaviour in isolates. The observation cages were cleaned and their floors were covered with new wood shavings after each interaction.

Altogether 3 to 5 interactions were repeated 1 week apart with 404 pairs of singly- versus group-housed mice. Each isolate was paired with the same group-housed partner throughout the whole experiment. The isolates were given drugs or water 30 min before each interaction in a randomized order according to a Latin square design (each mouse served as its own control). The group-housed mice were given only water. All drugs except scopolamine were given orally; scopolamine was injected intraperitoneally.

Measurements

The incidence of the following behavioural acts and postures similar to those described by Grant & Mackintosh (1963) was recorded by a keyboard-counters system.

Sociable activities: Social sniff: sniffing the partner's head, body, genitals or tail. Climb: the mouse places its forepaws on the partner's back, mostly in the shoulder region, and usually sniffs this area at the same time (Grant & Mackintosh called this Attempted Mount). Follow: following the partner by quiet walking.

Timid activities (active flight): Alert posture: sudden interruption of all movements with eyes and ears being directed towards the other mouse (Attend, Freeze). Escape: a rapid running or jumping away from the opponent (Retreat and Flee). Defence: the mouse responds to the partner's social behaviour by raising the forepaws, hunching the back or by rearing up on the hind legs with the head and forelegs extended (Defensive or Submissive upright posture).

Aggressive activities: Attack: fierce lunging at the partner from various sides often associated with biting. Aggressive unrest: walking around the partner (Walk round, mince) or on its own axis (Circle), walking to and from the partner (To-fro) and chasing the partner. Tail rattle: rapid vibrations of the tail are classified as an ambivalent activity reflecting both aggressive and flight tendency.

Locomotion (non-social activities): Walk across cage: any walking which is apparently not related to the partner. Rear: the mouse stands only on his hind legs and usually sniffs air or walls at the same time.

The interobserver reliability of the recorded items was satisfactory, as determined by two observers recording independently behaviour of 18 mice in interactions lasting 200 s. The r_S values ranged from 0.7 to 0.8 ($P < 0.001$). Observers did not know which treatment was given to the tested animals.

Data analysis

Only the isolates exhibiting attacks in the control interaction were included in the present study. The differences between the control and experimental values were examined by the two-tailed Wilcoxon matched-pairs signed-ranks test (Siegel, 1956).

Results

Behaviour in control interactions

About 40% of isolates ($n = 162$) exhibited attacks in the control interaction. Behaviour of the aggressive isolates consisted largely of attacks, aggressive unrest, tail rattling and walking across the cage (Figure 1). Alert postures, sniffing partners and rearing were less frequent while defensive postures, escapes, climbing or following partners occurred very rarely in the aggressive isolates.

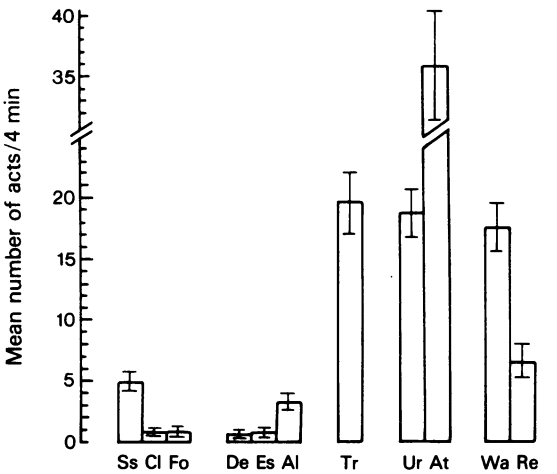

Figure 1 Behaviour of aggressive singly-housed male mice (n = 162) in the control paired interaction with non-aggressive group-housed male mice. Code for abbreviations: Ss = social sniffing, Cl = climbing over partner, Fo = following partner, De = defensive posture, Es = escape, Al = alert posture, Tr = tail rattling, Ur = aggressive unrest, At = attack, Wa = walking across cage, Re = rearing. Limits of confidence of means for P = 0.05 are given.

The rest of the isolates (about 60%, n = 242) which did not attack their partners in the control interaction are not included in the present study. Effects of drugs on behaviour of some of the non-aggressive isolates, which exhibited escapes or defensive postures but no attacks in the control interaction ('timid' mice) have been described in an earlier paper (Kršiak, 1975).

Group-housed mice never attacked the aggressive isolates, nor did they show aggressive unrest or tail rattling. The activity of group-housed mice was largely composed of defensive postures and escapes as passive responses to aggressive behaviour of their partners. Group-housed mice also showed a smaller amount of locomotion (walking across cage and rearing) and a few alert postures while their active social behaviour was limited to occasionally approaching and sniffing the aggressive isolates.

Effects of drugs on behaviour of aggressive isolates

Scopolamine and (+)-amphetamine reduced the incidence of attacks, aggressive unrests and of tail rattles after a comparatively low dose (0.25 mg/kg) which did not change significantly the amount of walking across the cage or rearing (Figures 2 and 3). Aggressive mice injected with scopolamine (0.25 mg/kg) showed more social sniffing while those given (+)-amphetamine (0.25 mg/kg) exhibited more escapes. Also the higher doses of scopolamine and

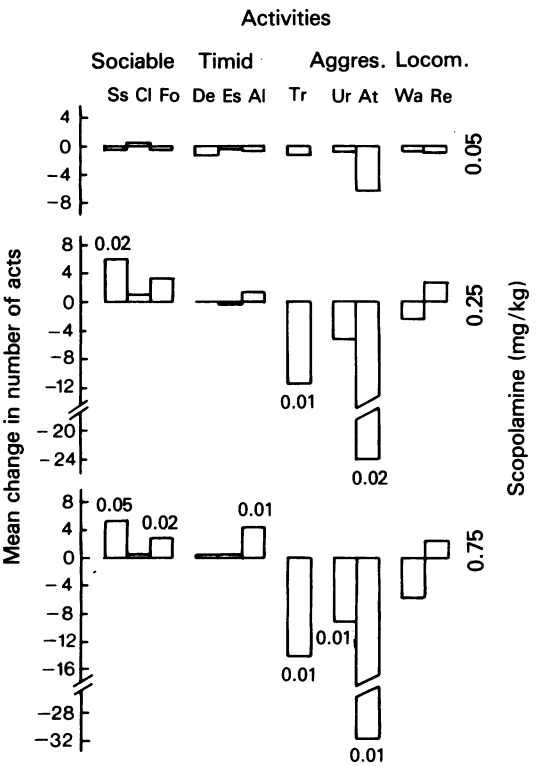

Figure 2 Behaviour of singly-housed aggressive mice given scopolamine in paired interactions with non-aggressive group-housed mice. The ordinate scale shows the number of acts during 4 min expressed as the mean difference from activity in the control interaction (which did not differ significantly from that depicted in Figure 1). Effects of each dose represent mean results from 8 to 12 aggressive mice.

of (+)-amphetamine (0.75 and 1 mg/kg, respectively) significantly reduced attacks, aggressive unrest and tail rattles without markedly changing incidence of locomotor activities (Figures 2 and 3). Scopolamine at a dose of 0.75 mg/kg increased the incidence of sniffing and following partners and also that of alert postures. On the other hand, 0.05 mg/kg of scopolamine did not produce significant changes.

Chlorpromazine also reduced the number of attacks and of tail rattles at a dose (2.5 mg/kg) which did not significantly inhibit incidence of locomotor activities (Figure 4). However, a somewhat higher dose of chlorpormazine, 7.5 mg/kg, reduced not only aggressive activities but also walking across the cage. A lower dose of chlorpromazine (0.75 mg/kg) was ineffective.

Diazepam and chlordiazepoxide significantly reduced the number of attacks only at the comparatively high doses of 10 and 50 mg/kg, respectively

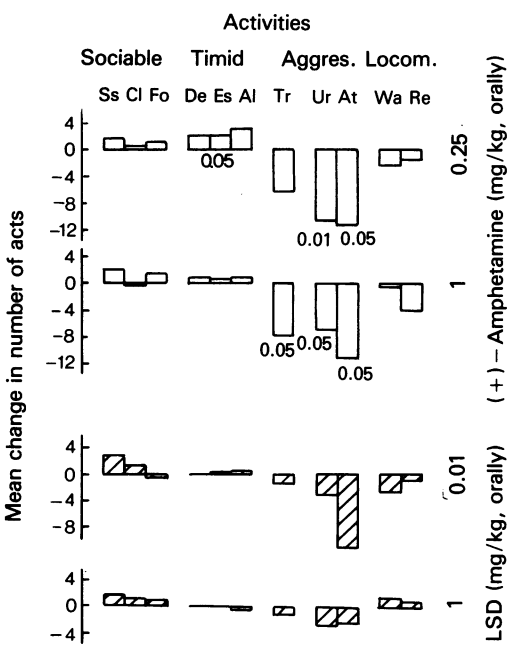

Figure 3 Behaviour of singly-housed aggressive mice given (+)-amphetamine or LSD in paired interactions with non-aggressive group-housed mice. Scale as for Figure 2. Effects of each dose represent mean results from 8 to 18 aggressive mice.

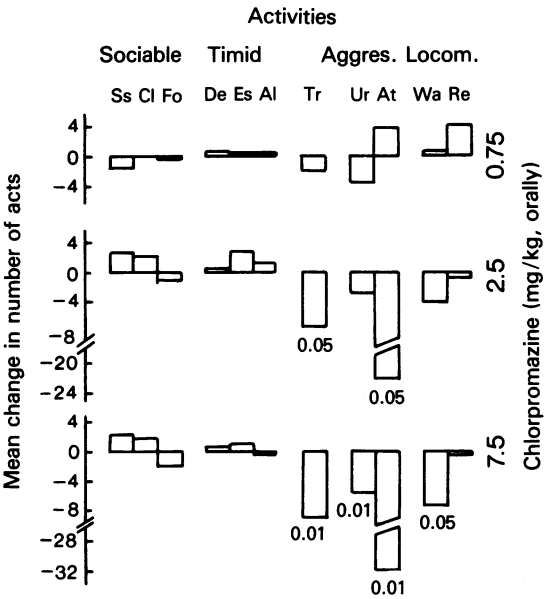

Figure 4 Behaviour of singly-housed aggressive mice given chlorpromazine in paired interactions with non-aggressive group-housed mice. Scale as for Figure 2. Effects of each dose represent mean results from 9 aggressive mice.

(Figures 5 and 6). However, neither of the high doses of diazepam and chlordiazepoxide (10 and 50 mg/kg respectively) significantly reduced locomotion (walking across cage, rearing) in the aggressive males; in fact, sociable activities (social sniffing and climbing) were significantly increased. In contrast to attacks, tail rattling was significantly reduced after the low doses of 1 and 5 mg/kg of diazepam and chlordiazepoxide, respectively (Figures 5 and 6). The reduction of tail rattling after 5 mg/kg of chlordiazepoxide was associated with a significantly increased aggressive unrest. Tail rattling was also significantly reduced after 5 and 20 mg/kg of diazepam and chlordiazepoxide, respectively, which significantly increased the occurrence of some sociable activities (Figures 5 and 6). The lowest doses of diazepam and chlordiazepoxide tested (0.2 and 1 mg/kg, respectively) produced no significant changes.

Imipramine significantly reduced attacks and other aggressive activities only at a high dose (80 mg/kg) which decreased walking across the cage and rearing (Figure 7). Barbitone (Figure 7) and lysergic acid diethylamide (LSD, Figure 3) did not significantly reduce attacks at any dose tested (20 and 60 mg/kg or 0.01 and 1 mg/kg, respectively). In contrast, barbitone tended to increase the incidence of attacks. The higher dose of barbitone (60 mg/kg) significantly increased the incidence of sniffing and following partners (Figure 7).

Discussion

Scopolamine decreased the incidence of attacks at a low dose (0.25 mg/kg) without inhibiting walking across the cage or rearing in aggressive mice. Low doses of scopolamine not producing signs of neurotoxicity also reduced intraspecies attacks in mice in other studies (e.g. Janssen, Jageneau & Niemegeers, 1960; DaVanzo, Daugherty, Ruckart & Kang, 1966). Scopolamine has also been reported to reduce species-specific attacks and some other agonistic and non-agonistic social activities in rats at doses from 0.1 mg/kg which did not influence exploration of the cage (Van der Poel & Remmelts, 1971). With a high baseline of aggression, scopolamine reduced the number of aggressive activities in squirrel monkeys at doses as low as 0.005 to 0.05 mg/kg (Plotnik, Mollenauer, Gore & Popov, 1975). In the present study, the higher dose of scopolamine (0.75 mg/kg) increased the incidence of alert postures. This finding is in agreement with the study of Plotnik *et al.* (1975) who found an increased visual scanning and startle-ability in scopolamine-treated monkeys. Taken together, the

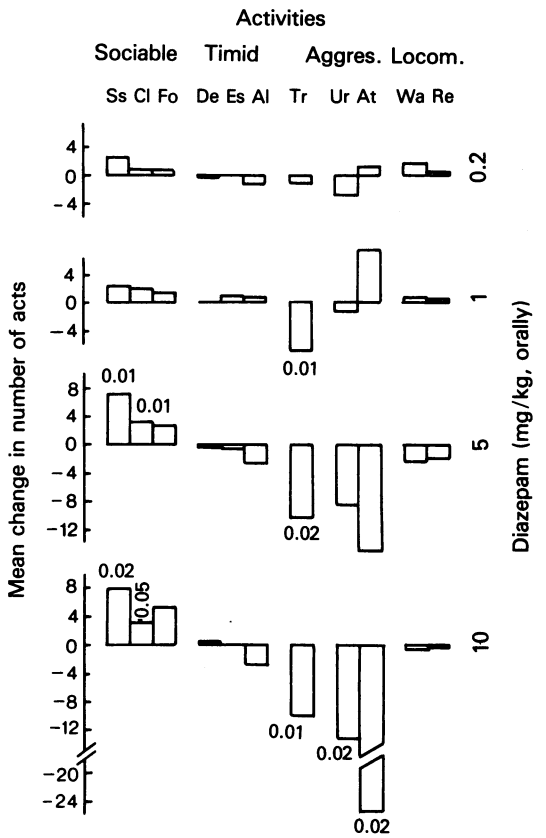

Figure 5 Behaviour of singly-housed aggressive mice given diazepam in paired interactions with non-aggressive group-housed mice. Scale as for Figure 2. Effects of each dose represent mean results from 8 to 14 aggressive mice.

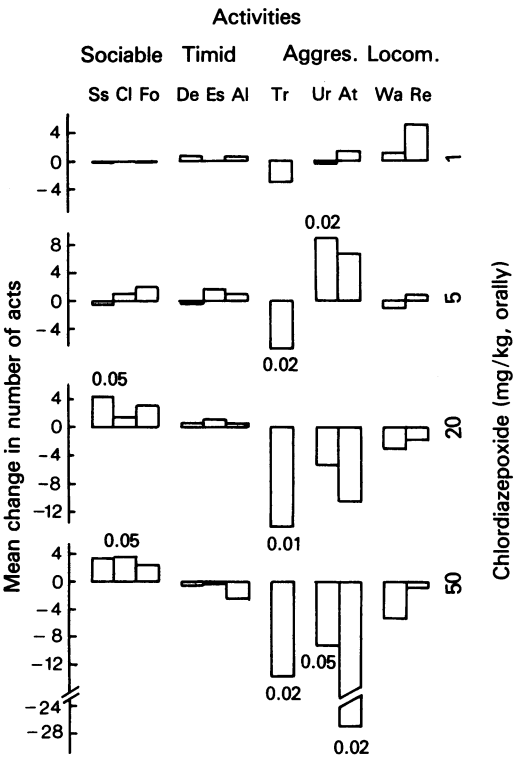

Figure 6 Behaviour of singly-housed aggressive mice given chlordiazepoxide in paired interactions with non-aggressive group-housed mice. Scale as for Figure 2. Effects of each dose represent mean results from 8 to 13 aggressive mice.

present findings agree with other reports indicating that scopolamine markedly reduces intraspecies aggression at comparatively low doses which do not produce general inhibition of motor activity.

On the other hand, the present finding of a significant reduction in frequency of attacks after a low dose of (+)-amphetamine (0.25 mg/kg) is in contrast with a number of studies reporting a decrease of attacks in mice only after 3 to 8 mg/kg of (+)-amphetamine (e.g. Le Douarec & Broussy, 1969; Welch & Welch, 1969; Zwirner, Porsolt & Loew, 1975). Other studies found no change or an increase of intermale aggression in mice after 2 to 5 mg/kg of (+)-amphetamine (DaVanzo *et al.*, 1966; Valzelli, Giacalone & Garattini, 1967; Welch & Welch, 1969). Recently, however, Miczek & O'Donnell (1978) have reported reduction of intraspecies attacks in mice given 0.5 to 2 mg/kg of (+)-amphetamine. The latter study suggests that the discrepancy in sensitivity to the agression-reducing effect of (+)-amphetamine between the present and the earlier studies may be due to differences in the recipients of the drug treatment: (+)-amphetamine was given only to test animals in the present and the Miczek & O'Donnell study, while it was given to both or all interacting animals in the others (Valzelli *et al.*, 1967; Le Douarec & Broussy, 1969; Welch & Welch, 1969, Zwirner *et al.*, 1975). Amphetamine-like drugs given to stimulus mice can indirectly increase aggression in non-treated test mice (Miczek, 1977; Miczek & O'Donnell, 1978).

Low doses of amphetamine or methamphetamine (0.125 to 1 mg/kg) given exclusively to the test animal also reduced intraspecies aggressive behaviour in rats (Silverman, 1966a; Miczek, 1974), cats (Hoffmeister & Wuttke, 1969) and monkeys (Crowley, Stynes, Hydinger & Kaufman, 1974), although in monkeys this was associated with stereotypies, hyperactivity and social unrelatedness. In the present study, no apparent stereotypies were observed after 0.25 and 1 mg/kg of (+)-amphetamine. The lower dose of (+)-amphetamine (0.25 mg/kg) also increased escapes which

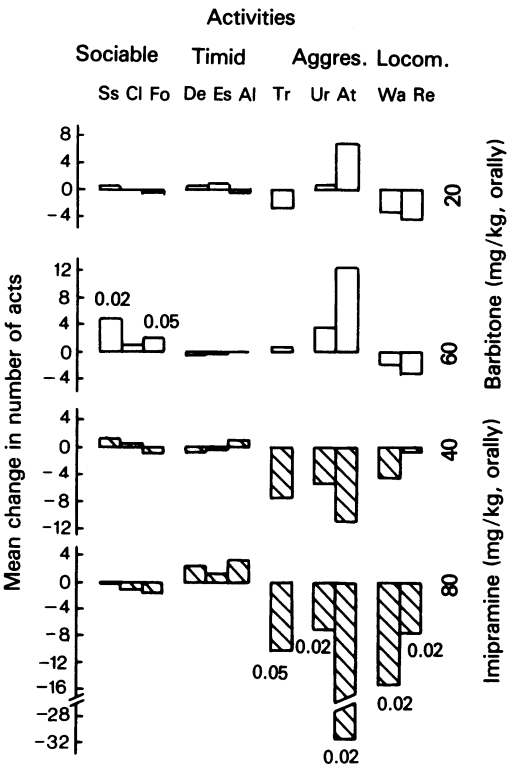

Figure 7 Behaviour of singly-housed aggressive mice given barbitone or imipramine in paired interactions with non-aggressive group-housed mice. Scale as for Figure 2. Effects of each dose represent mean results from 8 to 20 aggressive mice.

agrees with other reports in mice (Kršiak, 1975; Miczek & O'Donnell, 1978; Kršiak & Přibík, 1978) and with (±)-amphetamine in rats (Silverman, 1966a). Thus, amphetamine appears to be able to reduce intraspecies aggression in mice at low doses not producing stereotypies. This effect may be associated with increased flight.

An oral dose of 2.5 mg/kg of chlorpromazine, which did not reduce social investigation or exploration of the cage, significantly reduced the incidence of attacks and tail rattles while moderately increasing timid activities in the present study. Thus, the reduction of aggression induced by chlorpromazine in the isolates does not seem to be due to a neuromuscular impairment and from this point of view it seems to be relatively specific. However, a somewhat higher dose (7.5 mg/kg) of chlorpromazine reduced not only aggressive activities but also walking across the cage, which suggests that the margins between doses inhibiting aggression and those reducing locomotion are relatively narrow. In fact, the activities most affected by the inhibitory action of chlorpromazine (attacks, tail rattles, aggressive unrests and walks across cage) were those with the highest control frequency which suggests a rate-dependent character of the antiaggressive effect of chlorpromazine.

Chlorpromazine was reported to inhibit intraspecies aggression in mice in a number of studies but it is rather difficult to judge the specificity of this effect. Thus, in many studies, where chlorpromazine was given to both or all interacting animals (e.g. Valzelli *et al.*, 1967; Sofia, 1969), the reported inhibition of fighting might have been influenced by possible changes of behaviour in chlorpromazine-treated partners, as aggression of untreated test mice can be significantly reduced by interaction with chlorpromazine-treated opponents (Cairns & Scholz, 1973). Some authors do not mention this point (e.g. Gray, Osterberg & Rauth, 1961; DaVanzo *et al.*, 1966). In studies where chlorpromazine was given to test mice only, disparate indices of neurotoxicity yield contradictory conclusions on specificity. For instance, Hoffmeister & Wuttke (1969) and Dubinsky, Robichaud & Goldberg (1973) found similar effective doses of chlorpromazine for abolishing attacks in mice (2.35 and 2 mg/kg, respectively) in similarly designed experiments. In one study the reduction of aggression appears to be quite specific (climbing on an inclined screen was inhibited only after 14.3 mg/kg of chlorpromazine, Hoffmeister & Wuttke, 1969), but in the latter study the rota-rod performance was already impaired after 0.7 mg/kg of chlorpromazine.

The present results are in agreement with the effect of chlorpromazine on behaviour of previously isolated male rats in paired interactions with untreated male opponents (Silverman, 1965; 1966a). Chlorpromazine at 0.5 to 4 mg/kg, reducing overall activity, particularly reduced aggression, social investigation and mating, and actually increased flight, while exploration of the cage was rarely affected. The reduction of aggressive acts and postures was probably not due to neuromuscular impairment since activities posturally similar but behaviourally different were not affected in the same way.

Diazepam and chlordiazepoxide reduced attacks and aggressive unrest only at the relatively high doses of 10 and 50 mg/kg, respectively. However, the frequency of other upright- or walk-type movements was unchanged (walking across the cage or rearing) or even increased (climbing over the partner) by these doses, which suggests that the reduction of attacks and of aggressive unrests was not due to a generally reduced ability to raise the front part of the body or to walk. Furthermore, the control frequency of agressive unrest, which is composed only of activities involving walking, and that of walks across cage was almost the same, so that the much stronger inhibition of aggressive unrest is not easily explained in terms of rate-dependence.

The literature on effects of benzodiazepines on intraspecies aggression in mice is voluminous but equivocal. Some studies suggest a specific inhibition of aggression (Scriabine & Blake, 1962; Cole & Wolf, 1966; Valzelli *et al.*, 1967; Le Douarec & Broussy, 1969; Robichaud, Gylys, Sledge & Hillyard, 1970; Valzelli, 1973) while others indicate the opposite (e.g. DaVanzo *et al.*, 1966, Hoffmeister & Wuttke, 1969; Sofia, 1969). However, none of these studies compared effects of benzodiazepines on aggressive and non-aggressive activities in the same mouse and experiment, or avoided confounding direct pharmacological effects with those induced by interaction with drugged partners at the same time. Control over the direct and indirect effects of benzodiazepines seems to be important as aggression of undrugged aggressive mice and rats can be increased by interaction with chlordiazepoxide-treated non-aggressive opponents (Borgesová, Kadlecová & Kršiak, 1971; Miczek, 1974). It is therefore difficult in most studies cited above to assess how far the direct diazepam- or chlordiazepoxide-induced inhibition of aggression was affected by a possible indirect stimulation of this behaviour through interaction with drugged partners. Furthermore, the varied tests of neurotoxicity used such as reduced walking on a rota-rod (Sofia, 1969; Valzelli, 1973), climbing on an inclined screen (Hoffmeister & Wuttke, 1969; Robichaud *et al.*, 1970) or escaping an electric shock (Cole & Wolf, 1966) give contradictory estimates of inability to perform aggressive activities. The present results suggest that the direct inhibition of aggressive behaviour, though produced by relatively high doses of diazepam and chlordiazepoxide, is not necessarily due to a general impairment of the ability to perform specific coordinated behavioural activities. High doses of chlordiazepoxide, not producing a general deficit of performances, also reduced intraspecies aggression in carefully controlled studies in rats (Miczek, 1974) and hamsters (Poole, 1973).

The lower doses of diazepam and chlordiazepoxide (1 and 5 mg/kg, respectively) moderately increased frequency of attacks, and 5 mg/kg of chlordiazepoxide stimulated aggressive unrest significantly in the present study. Low doses of chlordiazepoxide given to all interacting animals were reported to increase intraspecies aggression in mice (Fox, Tuckosh & Wilcox, 1970; Zwirner *et al.*, 1975). The present experiments indicate that intraspecies aggression can be increased directly in mice by administration of a low dose of chlordiazepoxide to the test animal only, as reported also in rats (Miczek, 1974) and in monkeys (Apfelbach & Delgado, 1974).

Tail rattling was markedly more sensitive towards the inhibitory action of benzodiazepines than attacks; diazepam and chlordiazepoxide reduced tail rattling significantly at doses of only 1 and 5 mg/kg, respectively, which were ten times lower than those inhibiting attacks, much as Le Douarec & Broussy (1969) also found. The other drugs tested in the present study inhibited tail rattling only at doses reducing attacks. It has been suggested that tail rattling occurs in situations in which the mouse is hesitating between attacking and escaping (e.g. Scott & Fredericson, 1951; Grant & Mackintosh, 1963; Crowcroft, 1966). Tail rattling has also been observed in mice when they were prevented from approaching food (Crowcroft, 1966) as well as in mice hesitating to approach a novel object (Poshivalov, 1978). Accordingly, tail rattling may reflect a more general conflict between approach and avoidance behaviour. The present finding that diazepam and chlordiazepoxide are very active in inhibiting tail rattling is therefore in good agreement with a widely held view on the strong anti-conflict activity of benzodiazepines.

Neither of the doses of barbitone tested reduced aggressive activities. Similarly phenobarbitone did not reduce attacks significantly even after 80 mg/kg given orally 60 min before test (Tomašíková & Kršiak, unpublished results). This is in line with most of the experimental literature (Yen, Stanger & Millman, 1959; Janssen *et al.*, 1960; Gray *et al.*, 1961; Cole & Wolf, 1966; DaVanzo *et al.*, 1966, Kletzkin, 1969; Sofia, 1969; Le Douarec & Broussy, 1969; Zwirner *et al.*, 1975). Only hexobarbitone was found to produce a total inhibition of aggressive behaviour in mice at a dose producing no 'signs of overt neuromuscular impairment' (Valzelli *et al.*, 1967).

Barbitone tended to increase the number of aggressive activities in aggressive mice as it does in timid mice (Kršiak, 1975). Le Douarec & Broussy (1969) also observed stimulation of attacks and tail rattles in mice with a low dose of pentobarbitone given to all interacting animals. Such stimulation could hardly have been detected in the other published studies since all but two (Kletzkin, 1969; Zwirner *et al.*, 1975) used maximum baselines of aggression. Barbiturates can also increase aggression in mice indirectly by interaction with drugged partners (Kršiak & Steinberg, 1969). In a carefully controlled study, barbiturates given to the test animal also increased aggression in rats (Silverman, 1966b).

Imipramine reduced aggressive activities only at a high dose (80 mg/kg) which also inhibited walking across the cage and rearing. Imipramine thus seems to lack a specific antiaggressive potency in mice which is in agreement with the published data (Cook & Weidley, 1960; DaVanzo *et al.*, 1966; Valzelli *et al.*, 1967; Boissier, Grasset & Simon, 1968; Sofia, 1969).

LSD (0.01 and 1 mg/kg) did not significantly change aggressive or other activities in the present study. Other studies also failed to find a uniform specific effect of LSD on intraspecies aggression in mice. Pairs or groups of mice given 0.002 to 0.5 mg/kg

of LSD were reported to show head-twitches, vegetative changes, increased social withdrawal, flight and self-grooming and a lower or unchanged amount of aggression (Uyeno, 1966; Valzelli *et al.*, 1967; Siegel & Poole, 1969). Increased flight, tail rattling and overall activity after LSD was found in timid mice (Kršiak, Borgesová & Kadlecová, 1971; Kršiak, 1975). It seems that many LSD-induced changes of social behaviour, involving occasional stimulation of aggression (Kršiak *et al.*, 1971) result from a general enhancement of reactivity or responsiveness (Siegel & Poole, 1969).

Scopolamine (0.25 and 0.75 mg/kg), diazepam (5 and 10 mg/kg), chlordiazepoxide (20 and 50 mg/kg) and barbitone (60 mg/kg) significantly increased sociable activities in aggressive mice whereas (+)-amphetamine, chlorpromazine, imipramine and LSD did not, which is in good agreement with effects of the drugs on sociable behaviour in timid mice (Kršiak, 1975). Stimulation of social investigation on encounters between strange males was also found after an anticholinergic drug and barbiturates in rats (Silverman, 1966a, b) and benzodiazepines in hamsters (Poole, 1973). It is of interest that the present findings are to some extent in agreement with effects of the drugs on suppressed operant behaviour. Thus, benzodiazepines and barbiturates mostly increase rate of responding suppressed by an aversive stimulus (e.g. rewarded lever pressing suppressed by electric shock, Geller & Seifter, 1960) while phenothiazines, imipramine, amphetamine and hallucinogens usually do not increase it (Kelleher & Morse, 1968; MacMillan, 1975). Scopolamine, however, attenuated only some types of suppressed operant responding (Berger & Stein, 1969). It is conceivable that the strange male represents an aversive stimulus which suppresses sociable behaviour in aggressive and timid mice. Both aggressive and timid singly-housed mice showed a lower control frequency of sociable activities than those exhibiting neither aggressive nor timid responses to the strange male ('sociable' mice, Kršiak, 1975). Also, their control frequency of sociable activities was lower than that of aggressive or timid or locomotor activities. Testing effects of drugs on suppressed social investigation on agonistic intermale encounters in mice might be helpful in evaluation of behavioural activity of drugs similarly to some commonly used methods of punished responding.

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