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ORIGINAL INVESTIGATION

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Differential effects of chlordiazepoxide on aggressive behavior in male mice: the influence of social factors

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Abstract The present study examined the influence of prior social experience on the effects of chlordiazepoxide (CDP; 5.0, 10.0 and 20.0 mg/kg) on intrasexual aggression in male mice. Prior to drug testing, animals were either individually housed or screened in dyadic encounters in a neutral cage. This novel method yielded four experimental groups comprising animals with different social experiences and different aggressive/defensive characteristics: 1) individually-housed males (I): 2) aggressive males (A); 3) counter-attacking males (C), which actively responded to but did not initiate attack; and 4) defeated males (D). Twenty-four hours after screening, animals were treated with CDP and subjected to a resident-intruder test with untreated intruders. Results indicated that the lowest dose of CDP (5 mg/kg) increased aggressive behaviour but only in A males. At higher doses (10–20 mg/kg), CDP reduced attacks towards intruders in A, C and I, but not D, males. In A and C males, the antiaggressive action of CDP was associated with a prosocial effect (increased social investigation), whereas in I males, reduced aggression was associated with an increase in fear-related behaviours. As these differential effects of CDP on intermale aggression cannot be fully explained by differences in behavioural baselines, present data highlight the importance of experiential background as a powerful variable in determining behavioural responses to benzodiazepines. Present findings therefore suggest that an understanding of drug effects on social behaviour demands consideration of biological variability in phenotype.

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Introduction

Many drugs acting at the GABAA/benzodiazepine receptor complex have been shown to play an important role in the modulation of aggressive, defensive and social behavior. For example, benzodiazepines (BDZ) have been consistently found to reduce aggressive behavior in a large number of species (for review: see Rodgers 1991; Miczek et al. 1995). However, at lower doses especially, these compounds have been also been reported to produce "paradoxical" increases in aggression (Miczek 1974; Krsiak 1975; Miczek and O'Donnell 1980; Rodgers and Waters 1985; Yoshimura and Ogawa 1989; Olivier et al. 1991; Palanza et al. 1996), effects that may be related to basal levels of aggression and/or anxiety (Mos and Olivier 1987; Blanchard et al. 1989; Rodgers 1991). Interestingly, other drugs which act at the GABAA receptor complex (such as ethanol) also produce biphasic effects on aggressive behavior in various species (for review, see Miczek et al. 1994a). The involvement of a common substrate in these actions is suggested by the observation that the pro-aggressive effects of ethanol and BDZ in mice interact in an additive manner (Miczek and O'Donnell 1980), while the pro-aggressive effects of ethanol in rats and squirrel monkeys are blocked by the benzodiazepine receptor antagonists flumazenil and ZK 93426 (Weerts et al. 1993; Miczek et al. 1994b). As BDZ have been found occasionally to induce marked irritability, hostility and assaultive behavior in humans (Di Mascio 1973; Kochanzky et al. 1977; Simon and Lecrubier 1982; Bond and Lader 1988; Brizer 1988; Cutler et al. 1996), their "paradoxical" effects on animal aggression may be of particular relevance to clinical problems related to treatment of

aggressive and violent patients (Miczek et al. 1994b). Despite the above findings, however, there is a wealth of literature that has failed to find evidence of increased aggression in animals treated with BDZ (Krsiak et al. 1981; Poshivalov 1981; Skolnick et al. 1985; Krsiak and Sulcova 1990; Everill et al. 1991; Martin-Lopez and Navarro 1996). Although such inter-laboratory discrepancies could be attributed to multiple organismic and procedural variables (e.g. different species, strains or models of aggression), recent reports have specifically focused upon individual differences in responses to social stimuli and/or drug treatment (Miczek et al. 1994a; Ferrari et al., submitted). For example, prior social experience can strongly affect the propensity for individuals to show aggressive responses (Blanchard and Blanchard 1981; Brain 1981; Winslow and Miczek 1984), while there are clear indications that social history may be an important determinant of BDZ action in modulating social behavior (e.g. Miczek 1974; Olivier and Van Dalen 1984). It is therefore very relevant to note that Palanza et al. (1996) have recently shown that the effects of a single aggressive experience during lactation strongly influences the effects of chlordiazepoxide on maternal aggression in mice. In view of these potentially important findings, the aim of the present study was to investigate the effects of chlordiazepoxide on intermale aggression in groups of mice differing with respect to prior social experience. A novel screening methodology allowed for the individual characterization of test subjects in advance of the pharmacological intervention. This was achieved on the basis of a single dyadic social encounter in a neutral cage, during which animals were observed to respond very differently to same-sex unfamiliar conspecifics. The observed patterns of interaction enabled identification of males with different social experiences and with different aggressive/defensive characteristics, and their responses to CDP treatment were subsequently (24 h) studied in home-cage confrontations with untreated intruders.

Materials and methods

Animals

Subjects (n = 147) were Swiss albino male mice (CD-1), born and reared in our lab from a stock originally purchased from Charles River Italia (Calco, Lecco). After weaning (28–30 days old), males were randomly assigned to one of two main conditions: (a) group-housed (eight to ten per cage; $45 \times 28 \times 13$ cm) with same-sex conspecifics and then screened for aggression against an unfamiliar same-sex conspecific, or (b) singly-housed (isolated – I) for about 1 month in transparent Plexiglas chambers ($27 \times 13 \times 12$ cm); with the exception of the experimental day, these animals were unhandled. All animals were housed in 12:12-h lighting regime (lights on at 0700 hours) throughout the experiment. Temperature was maintained at 20 ± 2°C and food and water were freely available.

Drug

Chlordiazepoxide hydrochloride (CDP; Sigma, St Louis Mo., USA) was dissolved in physiological saline (0.9%) which, alone, served for control injections. All injections were administered IP (10 ml/kg injection volume) 30 min before testing.

Screening test

At the age of 8 weeks, group-housed animals were individually placed in transparent Plexiglas chambers ($27 \times 13 \times 12$ cm). One day later, they confronted a 24-h individually housed, weight-matched, unfamiliar opponent in a neutral Plexiglas cage ($27 \times 13 \times 12$ cm). These dyadic encounters, which lasted for a maximum of 10 min, enabled identification of the following categories of mice: 1) positive aggressive experience; animals that attacked the opponent and delivered at least ten bites were scored as aggressive (A) and the test immediately terminated; 2) Negative aggressive experience; animals that received at least ten bites and showed clear submissive postures (up-right) were scored as defeated (D) and the test immediately terminated; 3) counterattacking; animals that did not initiate attack but which actively responded to attacks by the opponent were scored as counterattacking (C).

Procedure

Immediately after the screening and prior to drug-testing, all males were singly-housed in transparent Plexiglas chambers ($27 \times 13 \times 12$ cm) for a period of 24 h. The floor of the chamber (home cage) was covered by sawdust bedding, and food and water were freely available. On test days, males were further randomly allocated to one of the following treatment conditions:

1. Saline-Control (I, n = 10; A, n = 10; D, n = 8; C, n = 10)
2. 5.0 mg/kg CDP (I, n = 10; A, n = 11; D, n = 9; C, n = 9)
3. 10.0 mg/kg CDP (I, n = 10; A, n = 9; D, n = 8; C, n = 8)
4. 20.0 mg/kg CDP (I, n = 10; A, n = 9; D, n = 8; C, n = 8)

Thirty minutes after injection, an undrugged intruder (same sex, weight-matched and unfamiliar) was introduced into the residents' home cage for a 10-min test. Each resident was tested once only and test duration was timed from the moment of initial social contact. All tests were videorecorded by means of a VHS camera/cassette recorder situated 0.5 m above the apparatus.

Ethical considerations

Throughout this study, and in accordance with ASAB guidelines governing animal behaviour research (Elwood and Parmigiani 1992), care was taken to minimise any distress caused to the animals.

Behavioral analysis

Behavior was scored off videotape by a trained observer, who remained blind to treatment conditions until data analysis was completed. Data were logged by a series of electronic counters and timers. With the exception of attack latency and bite frequency, all measures were scored as duration(s). The following categories and elements of behaviour were recorded: a) proportion of intruders attacked; b) latency to attack (i.e. time from initial contact to first bite attack); c) accumulated attacking time [i.e. total duration of biting attack (AAT)]; d) number of bites; e) fear-related behaviours (summed duration of freezing evoked by intruder proximity, flight,

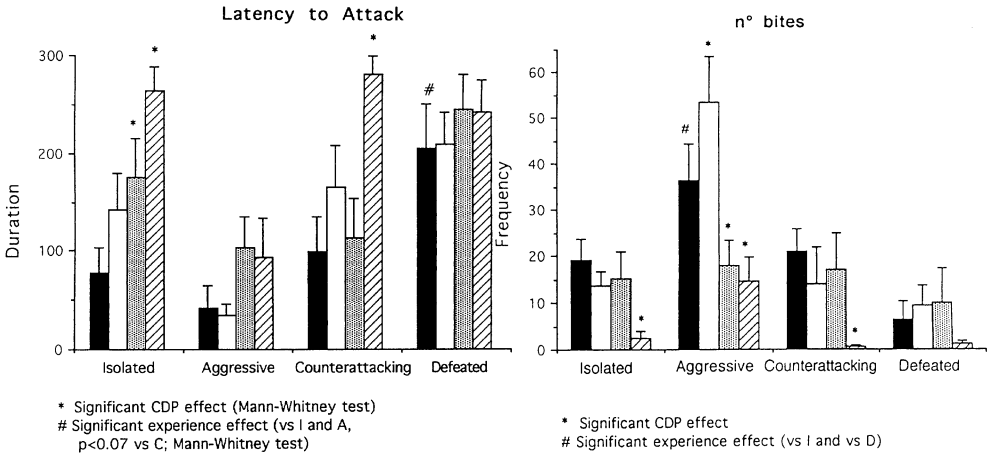

Fig. 1 Effects of CDP on latency to attack and number of bites towards strange intruders by males of different social experience. Data are presented as mean values (± SEM). ■ SAL, □ 5.0 mg/kg, ▨ 10.0 mg/kg, ▨ 20.0 mg/kg

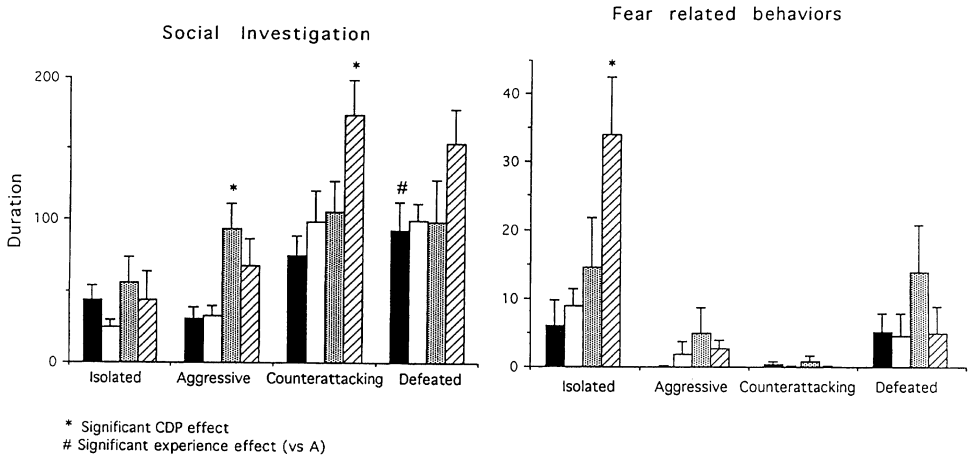

Fig. 2 Effects of CDP on social investigation and fear related behaviors shown by males of different social experience in response to male intrusion. Data are presented as mean values (± SEM). ■ SAL, □ 5.0 mg/kg, ▨ 10.0 mg/kg, ▨ 20.0 mg/kg

startle, upright and/or vocalization reactions in response to approach from or contact with intruder); f) self-grooming; g) social investigation; h) exploratory behavior; and I) immobility: inactivity unrelated to approach from or contact with the intruder.

Statistics

Data on the proportion of attacking experimental males andgroup-housed intruders were compared using the Fisher Exact Probability Test. Data on attack latency were also analyzed by non-parametric tests (Kruskal-Wallis followed, where indicated, by Mann-Whitney). All the other data (percent time, calculated on precise experimental time) were initially arcsin-transformed to give normal disrtibutions. These data were then analysed by a two-way independent parametric analyses of variance (factors = experience and drug treatment; 4 × 4 ANOVA). Unplanned comparisons were used for binary contrasts.

Results

Data are summarized in Figs. 1–3, and Tables 1 and 2.

Proportion of attack (Tables 1 and 2)

The proportion of attacking animals was not significantly affected by social experience although, as might be expected, the value recorded for D males was lower than those for the other categories (Table 1). In I and C (but not A or D) males, 20.0 mg/kg CDP significantly reduced the proportion of attacking animals ($P < 0.01$ and $P < 0.05$, respectively). As apparent from Table 2, attacks on residents by intruders were very infrequent and, importantly, the proportion of attacking intruders was unaffected either by the social experience or drug treatment of the residents.

Latency to attack (Fig. 1, left)

In the control condition, D males showed higher attack latencies than the other experimental categories (versus A, $z = -2.04$, $P < 0.05$; vs I, $z = -2.87$, $P < 0.005$; vs C, $z = -1.81$, $P < 0.07$). CDP treatment significantly affected attack latencies, but only in I and C males ($H = 13.72$, $P < 0.004$ and $H = 10.98$, $P < 0.02$, respectively). Further analysis showed that, while CDP dose-dependently increased attack latencies in I males (10 mg/kg; $z = -2.20$, $P < 0.03$ and 20 mg/kg; $z = -3.32$, $P < 0.0009$), only the higher dose significantly increased latencies in C males ($z = -2.94$, $P = 0.004$).

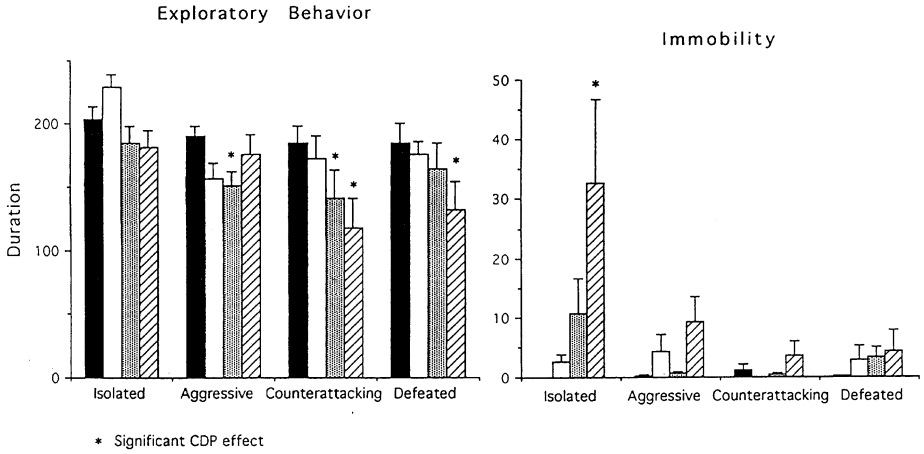

Fig. 3 Effects of CDP on exploratory behavior and immobility shown by males of different social experience in response to male intrusion. Data are presented as mean values (± SEM). ■ SAL, □ 5.0 mg/kg, ▩ 10.0 mg/kg, ▨ 20.0 mg/kg

Table 1 Effects of chlordiazepoxide on percentage of attacking males of different social experience confronting strange intruders

Drug treatment	Isolated	Aggressive	Counter attacking	Defeated
Saline	9/10	10/10	8/10	3/8
5.0 mg/kg	8/10	11/11	7/9	6/9
10.0 mg/kg	6/10	8/9	6/8	3/8
20.0 mg/kg	2/10*	7/9	2/8**	3/8

*$P < 0.01$ vs saline, **$P < 0.05$ vs saline

Table 2 Proportion of intruders attacking experimental resident males

Durg treatment	Isolated	Aggressive	Counter attacking	Defeated
Saline	0/10	3/10	1/10	1/8
5.0 mg/kg CDP	1/10	2/11	0/9	0/9
10.0 mg/kg CDP	0/10	1/9	2/8	1/8
20.0 mg/kg CDP	1/10	0/9	0/8	0/8

Accumulated attacking time (AAT) (data not shown)

ANOVA revealed significant main effects for experience ($F = 14.55$, $P < 0.0001$) and drug treatment ($F = 3.64$, $P < 0.02$), but no interaction. In the control group, A males showed significantly higher levels of AAT relative to D males ($F = 9.41$, $P < 0.003$) with similar (though non-significant) trends apparent versus I and C males $F = 2.86$, $P < 0.1$ and $F = 3.57$, $P < 0.07$ respectively). At the lowest dose tested, CDP increased AAT but only in A males (5.0 mg/kg; $F = 4.81$, $P < 0.03$) and, at the highest dose tested, decreased AAT but only in I males (20.0 mg/kg; $F = 5.03$, $P < 0.03$).

Bite frequency (Fig. 1, right)

ANOVA revealed a significant experience × drug interaction ($F = 2.14$, $P < 0.04$). In the control condition, A males showed a significantly higher number of bites compared to I and D males ($F = 4.30$, $P < 0.05$ and $F = 11.43$, $P < 0.001$, respectively), with a similar tendency also found relative to C males ($F = 3.36$, $P < 0.07$). In A males, bite frequency was increased by 5 mg/kg CDP ($F = 4.21$, $P < 0.05$), and reduced by 10.0 and 20.0 mg/kg CDP ($F = 4.57$, $P < 0.04$ and $F = 6.50$, $P < 0.02$, respectively). CDP 20.0 mg/kg also reduced the number of bites directed by I and C males towards intruders ($F = 4.26$, $P < 0.05$ and $F = 5.94$, $P < 0.02$, respectively).

Social investigation (SI) (Fig. 2, left)

ANOVA indicated significant main effects for experience ($F = 18.53$, $P < 0.0001$) and drug treatment ($F = 6.80$, $P < 0.003$), but no interaction. In the control condition, A males showed significantly lower levels of SI compared to D males ($F = 6.38$, $P < 0.02$). Moreover, there was a tendency for A males to show lower levels of SI versus C males ($F = 3.74$, $P < 0.06$) and for I males to show lower levels of SI versus D males ($F = 3.83$, $P < 0.06$). CDP treatment enhanced SI in both C (20.0 mg/kg; $F = 15.86$, $P < 0.0001$) and A (10 mg/kg; $F = 6.89$, $P < 0.01$) males.

Self-grooming

ANOVA did not reveal any significant effects.

Fear-related behaviours (Fig. 2, right)

ANOVA revealed a significant experience × drug interaction ($F = 2.90$, $P < 0.004$), with further analysis indicating that 20 mg/kg CDP increased fear levels in I males only ($F = 27.19$, $P < 0.0001$).

Exploratory behaviour (Fig. 3, left)

ANOVA revealed significant main effects for experience ($F = 7.13$, $P < 0.0002$) and drug treatment ($F = 6.27$, $P < 0.0005$), but no interaction. CDP decreased exploratory behaviour in A (10.0 mg/kg; $F = 4.60$, $P < 0.04$), C (10.0 and 20.0 mg/kg; $F = 4.17$, $P < 0.05$ and $F = 9.84$, $P < 0.003$, respectively) and D (20.0 mg/kg; $F = 4.86$, $P < 0.03$) males.

Immobility (Fig. 3, right)

ANOVA revealed a significant experience×drug interaction ($F = 2.22$, $P < 0.03$), with further analysis showing that 20.0 mg/kg CDP increased immobility in I animals only ($F = 28.65$, $P < 0.0001$).

Discussion

Present findings show that prior aggressive experience with same-sex unfamiliar conspecifics influenced subsequent aggressive responses in male Swiss mice. The profiles of the control groups basically confirms previous studies (Brain and Parmigiani 1990) in that males with positive aggressive experience (A) showed higher baseline levels of aggression and lower levels of social investigation compared to mice with negative social experience (D and, partially, C males). Furthermore, the baseline profile of individually housed mice (I) is more similar to that of the aggressive males than any other category. Although some differences between I and A mice were evident (i.e. A males showed a significantly higher number of bites relative to I males), this result is in accordance with the well-known physiological and behavioural similarities between isolated and aggressive-dominant mice (Brain & Benton 1977; Brain 1989; Parmigiani et al. 1980). In addition to these observations, and consistent with recent findings on maternal aggression (Palanza et al. 1996), current data show that prior social experience alters the effects of CDP on intermale aggression in Swiss mice. At higher doses, CDP reduced the proportion of attacking animals (20 mg/kg) and increased attack latencies (10–20 mg/kg); however, these effects were seen only in I and C males. The lack of effect of CDP on these indices in A males cannot be attributed to baseline factors since control values for these animals did not differ from those of I and C males. However, the absence of a drug effect on attack latencies and proportion of attacks in D males may be attributed to their lower basal aggressive tendency. Although CDP clearly reduced several other measures of aggression in I, A and C males (AAT and/or bite attacks), the mechanism responsible for these effects appears to be different. Thus, parallel to the observed decrease in aggressive behavior, A and C males showed a significant increase in social behaviour, whereas I males displayed increased fear-related behaviours and immobility. As these groups did not differ significantly in control levels of social investigation, fear-related behaviour or immobility, this differential pattern of CDP effects cannot simply be attributed to differences in behavioural baselines. Although the anti-aggressive action of BDZ is often associated with concurrent sedation (e.g. Rodgers and Waters 1985; Rodgers 1991; Weerts et al. 1993), our results suggest a more selective action of CDP under present test conditions. Indeed, the only evidence of possible sedation was the increase in immobility observed at 20 mg/kg in I animals. However, it is interesting to note that, at this dose, I males also showed a dramatic increase in fear-related behaviors and, particularly, of active forms of defensive behavior such as escape. This result is incompatible with a sedative interpretation and may instead be indicative of a shift from an aggressive to a defensive-fearful behavioural strategy. In this context, it is particularly relevant to note that BDZ have also been found to increase active defensive responses in male intruder rats (Piret et al. 1991). Importantly, although some authors (e.g. Dixon 1982) have reported that BDZ-treated animals are subjected to increased attack from their untreated partners ("indirect" drug effect), present data clearly show that the increase in fear-related behavior observed in CDP-treated I males is not associated with increased partner aggression and, therefore, most probably reflects a direct action of CDP on the defensive motivation of the treated animals.

Studies on the effects of BDZ on the behavior of isolated animals have indeed produced conflicting results (Poshivalov 1981; Skolnick et al. 1985; Martin-Lopez and Navarro 1996; Wongwitdecha and Marsden 1996). These studies have shown that early environmental influences (i.e. isolation at 30 days of age) affect not only the aggressive behavior of adult male mice but also the effects of CDP on social behavior. This supports the idea that social deprivation during particular stages in the development may have profound effects on adult social behavior (Holson et al. 1991; Wongwitdecha and Marsden 1996) and that the GABA-benzodiazepine system may be at least partly involved in the underlying mechanisms.

In direct contrast to the pattern of behavioural change observed in I animals, the antiaggressive effect of CDP in A and C males was associated with a concurrent increase in social behavior and a reduction in exploratory behaviour (a prosocial effect). This shift from aggressive to social interactions is similar to that observed in other studies with BDZ, in which male mice were subjected to several aggressive experiences (Miczek and O'Donnell 1980; Krsiak and Sulcova 1990). Also consistent with our results, Weerts et al. (1992) found that mice selectively bred for high or low aggressivity were differentially sensitive to the behavioral effects of CDP; in particular, increased social behaviour was observed only in high-aggressive mice. Although the absence of a CDP effect on social behavior in I males does not appear to be rate-dependent (control scores do not differ for I, A and C males), a high basal level of social investigation could be responsible for the lack of CDP effect in D males. However, it is pertinent to note that, in direct contrast to its well-described prosocial effects in certain rat anxiety models (e.g. File 1980), diazepam has recently been reported to be ineffective as an anxiolytic in socially-defeated intruder rats (Tornatzky and Miczek 1995). It is well known that, like alcohol and barbiturates, BDZ show a biphasic effect on aggressive behavior with stimulation at low doses and inhibition at high doses (Miczek 1974; Miczek and Krsiak 1979; Mos et al. 1987; Mos and Olivier 1989; Miczek et al. 1995). Some authors have suggested that BDZ-induced enhancement of aggression may occur more easily when animals are naive, are confronted with a more difficult situation, or have a low baseline level of aggression (Mos and Olivier 1988; Mos et al. 1987). Such pro-aggressive activity has been interpreted to be a rate-dependent phenomenon reflecting the disinhibitory effects of these compounds as a consequence of reduced fear (Miczek and O'Donnell 1980; Mos et al. 1987). According to this hypothesis, anxiety or fear can inhibit aggression and this influence is attenuated by the anxiolytic action of BDZ. Current results, however, show a more complex profile of CDP activity on aggressive behavior. According to the above hypothesis, any pro-aggressive effects of CDP should have been observed in those animals with lower baseline levels of attack. On the contrary, our findings revealed pro-aggressive effects only in those animals which had relatively high baseline levels of aggression (as a result of prior positive aggressive experience). As such, the pro-aggressive effect of low doses of CDP does not appear to be a rate-dependent phenomenon. However, the apparent inconsistency between present and previously reported results can be at least partly resolved by methodological considerations. Thus, in some previous studies, the pro-aggressive effects of BDZ have been found in animals that were screened for reliable levels of aggression prior to drug testing (Miczek and O'Donnell 1980; Mos and Olivier 1987, 1989; Mos et al. 1987). Alternatively, in other studies, repeated measures designs have been employed in which animals received different drug treatments on different days according to a random schedule (Yoshimura and Ogawa 1991), again introducing an important experiential element which was not fully considered in data interpretation. In this context, it is interesting to note that, more than 20 years ago, Apfelbach and Delgado (1974) reported that CDP increased aggressive responses in a dominant rhesus monkey, but not in a low-ranking group member; similar findings have since been reported for other BDZ (Delgado et al. 1976). More recently, in mice, Palanza et al. (1996) found that CDP increased maternal attack against male intruders if the dams had prior aggressive experience but decreased it if they were experientially naive. Although these authors proposed that prior fighting experience may alter GABA functioning in the brain, thus affecting the action of CDP, the specific nature of any such changes remains unclear. While it is possible that similar experientially induced changes in GABA functioning may account for present results, studies on the effects of ethanol on aggression offer another plausible interpretation. More specifically, several reports have demonstrated that the aggressive behaviour of dominant squirrel monkeys towards rivals is greatly increased after the administration of low acute ethanol doses (Winslow and Miczek 1985, 1988; Winslow et al. 1988; Weerts et al. 1992), and that this effect is linked to hormonal (i.e. testosterone) status (Miczek et al. 1993).

In the present study, positive aggressive experience may have resulted in a behavioral modification of males towards a more dominant-like phenotype. Thus, the screening procedure used may not only have provided a particular social experience for individual subjects, but could also have resulted in the selection of animals with particular genetic/hormonal characteristics which determined their responsivity to CDP. Consistent with this proposal, recent work from our laboratory (Ferrari et al., submitted) has shown similar plus-maze profiles for aggressive mice (prescreened during dyadic encounters in a neutral cage) and dominant males left undisturbed in group-housed cages with same-sex conspecifics. In conclusion, the present study highlights the importance of individual experiential background as a powerful variable in determining the behavioural responsivity of male mice to CDP. Specifically, our data provide further insights into the pro-aggressive effects of BDZ which may have relevance for individual variability in clinical responses to agents of this class. They also emphasize that the anti-aggressive effects of these drugs are not invariably accompanied by a stimulation of sociability but may, in certain instances, actually be related to an enhancement of defensive reactivity. From a methodological viewpoint, the screening approach employed facilitates evaluation of animals on the basis not only of their aggressive potential (as in more traditional paradigms) but also of their defensive

characteristics. Overall, the observed pattern of results confirms that an understanding of drug effects on behavior demands consideration of phenotypic variability (Palanza et al. 1994, 1996) and strongly suggests that more attention should in future be given to the impact of prior social experience in determining inter-individual variability in drug response.

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