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Maternal aggression in rats: Effects of chlordiazepoxide and fluprazine

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Abstract. Although maternal agression in rats is confined to a restricted post-partum period, the high and stable aggression level and the constancy of its behavioural structure make it an attractive experimental procedure for studying the behavioural effects of psychotropic drugs. Female rats were tested against naive male intruder rats for 5 or 10 min on post-partum days 3–9, during which aggression is stable.

Chlordiazepoxide (CDP; 5, 10 and 20 mg/kg, orally) had a biphasic effect on aggression; it increased aggression considerably at 5 and (to a lesser extent) at 10 mg/kg. At 20 mg/kg aggression returned to control level. CDP shortened the latency to the first attack at 5 mg/kg, but not at higher dosages. CDP enhanced aggression, particularly in the first 2 min of an encounter. It did not change the structure of the aggressive behaviour, but did induce a dose-dependent increase in feeding. Fluprazine (Flu; 5, 10 and 20 mg/kg IP), a specific antiaggressive (serenic) drug, induced a dose-dependent decrease in aggression and exerted its largest effect in the first 2 min of an encounter. In accordance with the reduced aggression, latencies to the first attack increased. Maternal aggression in rats represents an extension to other (male) aggression paradigms in psychopharmacology. First, it has no male counterpart. Secondly, the hormonal mechanisms underlying this behaviour differ from those of male aggression. Thirdly, the morphology of maternal aggression is different from that shown in male models of agonistic behaviour (e.g. resident-intruder). These features make maternal aggression an attractive paradigm for pharmacological studies of female behaviour.

Key words: Maternal aggression – Female aggression – Offense – Defense – Ethopharmacology – Fluprazine – Chlordiazepoxide – Serenics – Benzodiazepines – Rat

Studies on the psychopharmacological control of aggressive behaviour are largely confined to interactions between males. Several reasons exist for this preference: most male rodents show reliable levels of aggression after a short period of isolation or cohabitation with a female (Brain et al. 1980), thus permitting easy experimental procedures. Higher levels of aggression can be evoked by the formation of colonies of rats (Blanchard and Blanchard 1977; Lore et al. 1984). In such a situation, most aggression towards an intruder is performed by one male, usually denoted as the dominant α-male. In principle, two forms of agonistic behaviour can be observed in this test situation: 1) fighting related to dominance maintenance within the colony and 2) attacks on an intruder. Both forms may differ in their sensitivity to drug manipulation (Dijkstra et al. 1984). However, the colony model requires a lot of space and is not very convenient for frequent drug testing. The above mentioned models share the reliable levels of aggression, the rather constant hormonal situation of the male and the broad background knowledge of environmental and experimental factors influencing the behaviour (Lore et al. 1984).

There is a paucity of data with regard to female aggression. Under most circumstances females are less aggressive than males (De Bold and Miczek 1984). Moreover, complicating factors such as the oestrous cycle and interference with sexual behaviour have not encouraged the development of experimental procedures for psychopharmacological studies on female aggression. Although female aggression does occur in a colony situation where the males have been removed (Blanchard and Blanchard 1981; Blanchard et al. 1984; Miczek and De Bold 1983), the literature is far more extensive regarding postpartum or maternal aggression (cf. Svare and Mann 1983). Female rats, mice and hamsters exhibit high levels of aggression towards conspecific intruders during the first 10–14 postpartum days. In particular, mice have been used to study the various factors controlling agonistic behaviour (Svare and Gandelman 1976; Svare et al. 1981; Al-Maliki et al. 1980) (for reviews see: Svare 1977; Svare and Mann 1983; Floody 1983). In a previous study we tested two strains of rats for maternal aggression during the first 2 weeks postpartum. A fairly stable period with regard to aggression could be delineated from day 4 to 12. The first 2 postpartum days showed higher levels of aggression, while from day 12 on aggression declined dramatically (Mos et al. 1985). Detailed observations showed that the aggression did not change qualitatively over time, i.e. the topography of attacks remained similar over the test days. Thus, it was possible to employ this test situation to study the effects of psychoactive drugs using animals as their own control. We therefore studied the effects of two psychotropic drugs which are known to influence male aggressive behaviour, namely chlordiazepoxide (CDP), which may increase aggression at low dosages (Miczek and Krsiak 1979), and fluprazine (Flu), which decreases aggression dose dependently (Olivier et al. 1984a, b). Fluprazine ([2-[4-[3-(trifluoromethyl)phenyl)]-1-piperazinyl]-

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ethyl] urea hydrochloride), a phenylpiperazine derivative, belongs to a class of drugs, developed by Duphar, Holland, with specific antiaggressive properties in animal aggression models. Because of the behavioural specificity (lack of sedation, no impairment of social interactions) drugs from this class have been referred to as Serenics (cf. Bradford et al. 1984; Olivier et al. 1984a). The results show that maternal aggression can be increased (CDP) or decreased, (Flu) while many other behaviours remain largely unaffected.

Since maternal aggression has different characteristics from male aggression it is a valuable extension, both for psychopharmacological studies (Brain and Al-Maliki 1979) and for ethological studies on the biological significance and organisation of the various types of agonistic behaviour. Results of CDP and Flu treatment will be compared to those observed in male aggression models.

Material and methods

Subjects. Female rats of approximately 250–350 g (4–9 months old) were used. Two strains were used: TMD-S3 females (S3), derived from CPB-TNO at Zeist, The Netherlands and F1-females (F1) which were daughters from a breeding in our laboratory between TMD-S3 males and Wistar females.

Procedure. Experimental females were placed together with a breeding male (Wistar or S3-male) in their makrolon® home cage (30 × 20 × 15 cm). On the bottom of this cage an iron gauze was placed which enabled the collection of ejaculation plugs. After an ejaculation plug was detected the male was left for another week with the female, after which she was placed in the observation cage (40 × 30 × 30 cm) where she stayed for the rest of the experiment. This cage was provided with nesting material; food and water were always available. These cages were situated in the observation room under a reversed day-night rhythm (12L12D), night starting at 7:00 A.M. The day of birth was depicted as postpartum day 0.

Every parturient female was tested each day against a naive male Wistar intruder, which had a lower body weight (~25 g) than the female.

Tests were performed during the first part of the dark period (from 8:30 till 12.30 A.M.) under red light conditions and consisted of placing a male intruder in the female's home cage for 10 (Flu) or 5 min (CDP). The ongoing behaviour was videotaped and analyzed later. Each intruder was used once and was sacrificed immediately after the morning sessions with in IP overdose of pentobarbital, followed by shaving and describing the localizations of the wounds on wound charts (Mos et al. 1984a).

Behavioural observations and scoring. The behaviour of the female was scored using the methods as described by Olivier (1981). For the present experiments, 32 behaviour elements were distinguished. These 32 elements were divided into seven categories, each comprising several behaviour elements. The description of most elements is given in Olivier (1981); a short description of elements typical for maternal aggression is included here.

a) *Inactivity:* includes Sitting and Lying.
b) *Exploration:* includes Attention, Sniffing, Rearing, Locomotion, Marking, Feeding, Digging and Carrying.
c) *Body care:* includes Grooming/Washing and Shaking.
d) *Introductory Social Behaviour (ISB):* includes Moving towards, Sniffing intruder, Social Grooming and Crawling under.
e) *Aggressive Behaviour:* includes Bite Attack on Head, Bite Attack on Body, Lateral Threat, Upright Posture, Teeth chattering, Nipping, Pulling, Kicking, Lunge, and On Top.
   Bite Attack on head includes fierce biting on head and snout often causing severe wounds.
   Bite Attack on body consists of bites on all parts of the body except the head; these attacks are mostly directed to the back and often cause severe wounds.
   During both types of bite attacks clinches often occur.
   Upright posture (Offensive or defensive upright) may or may not be accompanied by boxing.
   Nipping is a very short and low intensity bite on the head of the opponent. Usually no wounds are inflicted.
   Pulling occurs when the opponent is held by the teeth and drawn through the cage.
   Kicking mostly occurs during or is intermingled with Lateral Threat, in which the animal kicks with a hindleg at the opponent.
   Lunge is a very rapid movement towards the opponent (chase), mostly followed by bite attacks.
   On Top (Full Aggressive Posture, Keeping Down) when the female holds down the opponent which lies on its back.
f) *Avoidance Behaviour:* includes Moving Away and Keeping Off.
g) *Pup Care:* including On Nest (with all elements occurring there, as suckling, licking of the pups, etc), carrying of the pups, and burying of the pups.

Besides the frequency and duration of the elements, we also noted the latency of the first attack (occurrence of bite attack on head or body, lunge, nipping or on top) and the number of attacks per min. In the CDP experiments the observation period was restricted to 5 min, because it appeared from previous experiments (Mos et al. 1985) that almost all aggression (90–95%) took place during this period.

Experimental design. Drug experiments (Flu and CDP) were performed on postpartum days 3, 5, 7 and 9. Each female obtained each dose of a drug (including vehicle) according to a latin-square design over the 4 postpartum days. Preceding (day 1 and 2), intervening (4, 6 and 8) and following (10, 11, 12 and 13) days were used both to establish an aggression baseline and as wash-out days. Fluprazine hydrochloride (Duphar, Weesp, Holland) (0, 5, 10 and 20 mg/kg) was dissolved in water (vehicle) and administered intraperitoneally 30 min before testing in a volume of 2 ml/kg body weight. Chlordiazepoxide. HCl (0, 5, 10 and 20 mg/kg) (Hoffman-La Roche, Basle, Switzerland) was suspended in 1% tragacanth (vehicle) and administered orally 60 min before testing in a volume of 5 ml/kg body weight. The pre-injection times and injection routes chosen were based on data derived from voltammetric and behavioural experiments (Mos et al. 1984b; Olivier et al. 1984a).

In the Flu experiment S3 females were used ($N=8$), in the CDP experiments F1 females ($N=12$). All females were primiparous.

Statistical analysis. Friedman analysis of variance was employed to detect overall significance, followed by Wilcoxon matched pairs comparison between the dosages. Kruskal-Wallis analysis was used to test for differences in the bite target areas after drug treatment.

Results

Chlordiazepoxide (CDP). Figure 1 shows the effects of CDP on the number of attacks, the number of wounds inflicted and the latency to the first attack. CDP had a significant effect on the number of attacks (Friedman's $\chi^2=16.8$; $df=3$; $P=0.0007$), revealing a biphasic effect. At 5 and 10 mg/kg a significant enhancement was evident [Wilcoxon; t(0 vs 5 mg/kg)=4, $P=0.003$; t(0 vs 10 mg/kg)=1, $P=0.002$; t(5 vs 20 mg/kg)=6, $P=0.0005$; t(10 vs 20 mg/kg)=2, $P=0.003$], whereas at 20 mg/kg no enhancement was present [t(0 vs 20 mg/kg)=23; $P=0.19$]. This CDP effect was even more pronounced when the number of attacks was expressed per unit of time after the first attack. The reverse occurred in the latency to the first attack ($\chi^2=7.1$; df=3; $P=0.06$), although this did not reach the acceptable level of significance.

There was no significant change in the number of wounds following CDP treatment ($\chi^2=5.5$; df=3; $P=0.13$), neither was a change observed in the distribution of the wounds over the intruder's body: head and upper back remained the main target areas.

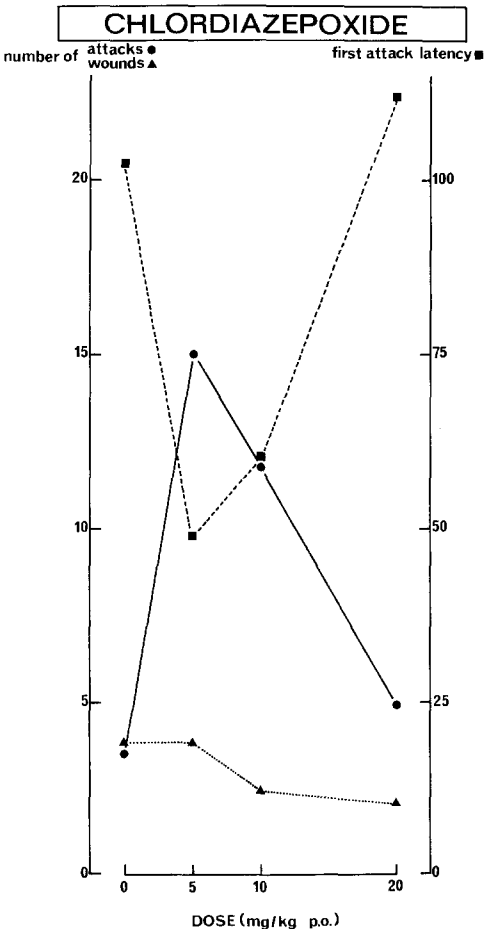

Fig. 1. Effect of chlordiazepoxide (0, 5, 10, and 20 mg/kg, orally) on the number of attacks (●), the number of wounds (▲) and the latency (s) to the first attack (■). Twelve females received each dose in a randomized order 60 min before testing

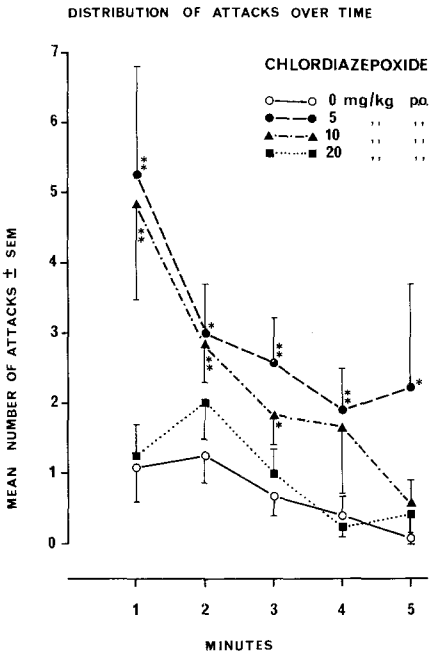

Fig. 2. Effect of different dosages of chlordiazepoxide on the distribution over time of the attacks in a 5-min maternal aggression test. Significant two-tailed differences from 0 mg/kg are depicted; * $P<0.05$; ** $P<0.02$

Figure 2 shows the decrease in attacks in the course of the 5-min encounter 60 min after CDP treatment. It is evident that the facilitatory effects of CDP (5 and 10 mg/kg) were most prominent during the first 2 min, although the overall levels of attack remained higher during the whole test period.

Table 1 shows the effects of CDP on seven behavioural categories in maternal aggression in the 5-min encounters with male intruder rats.

Exploration (in particular, the frequencies) showed a decreasing dose-dependent trend. In ISB an increasing trend was present in the duration data.

Aggression, both frequency and duration, showed biphasic effects; increases at 5 mg/kg and 10 mg/kg, and no difference compared to vehicle at 20 mg/kg PO.

The individual agonistic elements generally follow the same course (Fig. 3).

With the exception of Nipping, which peaked at 10 mg/kg, the other agonistic elements showed the highest levels at 5 mg/kg.

Although this test was specifically directed at measuring agonistic behaviour, we found an interesting and unexpected effect on feeding, which increased in a dose-dependent way (mean duration in s: 1.1, 8.2, 11.5, 26.0 for 0, 5, 10 and 20 mg/kg respectively). The stimulatory effect of CDP on feeding behaviour was very strong, because normally feeding was virtually absent in the 5-min test period.

Fluprazine (Flu). Figure 4 shows the effect of Flu on the number of attacks, the number of wounds inflicted and the latency to the first attack. Flu significantly reduced the number of attacks [$\chi^2=14.9$; df=3; $P=0.0013$; t(0 vs

Table 1. Effect of chlordiazepoxide on seven behavioural categories in maternal aggression of F_1 females

Behavioural categories	Dose of chlordiazepoxide (mg/kg, orally)				Friedman statistic		
	0	5	10	20		*df*	*p*-value
	Mean frequency ± SEM						
Inactivity	2.3 ± 0.6	1.0 ± 0.5	0.7 ± 0.3	1.3 ± 0.5	4.15	3	0.25
Exploration	67.8 ± 5.6	51.7[a] ± 6.2	39.0[b] ± 5.6	32.3[b,c] ± 2.9	14.5	3	0.0018
Body care	3.8 ± 0.8	1.8 ± 0.6	1.3 ± 0.2	2.9 ± 1.7	6.4	3	0.093
ISB	24.3 ± 2.2	34.5 ± 3.6	28.6 ± 3.1	25.6 ± 2.7	5.3	3	0.15
Aggression	8.1 ± 1.5	26.7[b] ± 5.8	17.5[a] ± 2.9	10.2[c,d] ± 2.2	11.7	3	0.0082
Avoidance	2.9 ± 1.5	1.3 ± 1.5	0.2 ± 0.1	0.3 ± 0.3	4.8	3	0.18
Pup care	4.8 ± 1.8	4.5 ± 1.1	5.0 ± 1.5	3.3 ± 1.3	0.7	3	0.88
	Mean duration (s) ± SEM						
Inactivity	10.6 ± 4.0	6.0 ± 3.5	9.6 ± 4.4	18.6 ± 8.8	1.2	3	0.76
Exploration	167.4 ± 14.8	129.9 ± 12.7	114.8 ± 14.7	119.7 ± 10.0	6.7	3	0.082
Body care	15.1 ± 3.5	5.4 ± 1.5	7.2 ± 1.6	12.1 ± 5.5	5.1	3	0.17
ISB	58.3 ± 3.0	87.5[b] ± 9.9	95.4[b] ± 12.2	108.9[b] ± 13.2	11.8	3	0.0077
Aggression	9.5 ± 1.9	36.3[b] ± 7.8	22.7[a] ± 4.9	15.1[a] ± 4.2	14.5	3	0.0018
Avoidance	4.9 ± 3.4	2.1 ± 1.4	0.2 ± 0.1	0.3 ± 0.2	3.6	3	0.30
Pup care	37.9 ± 14.2	37.4 ± 10.9	52.7 ± 14.7	26.1 ± 10.7	1.4	3	0.72

[a] Significant difference from 0 mg/kg at $P<0.05$
[b] Significant difference from 0 mg/kg at $P<0.01$
[c] Significant difference from 5 mg/kg at $P<0.05$
[d] Significant difference from 10 mg/kg at $P<0.05$

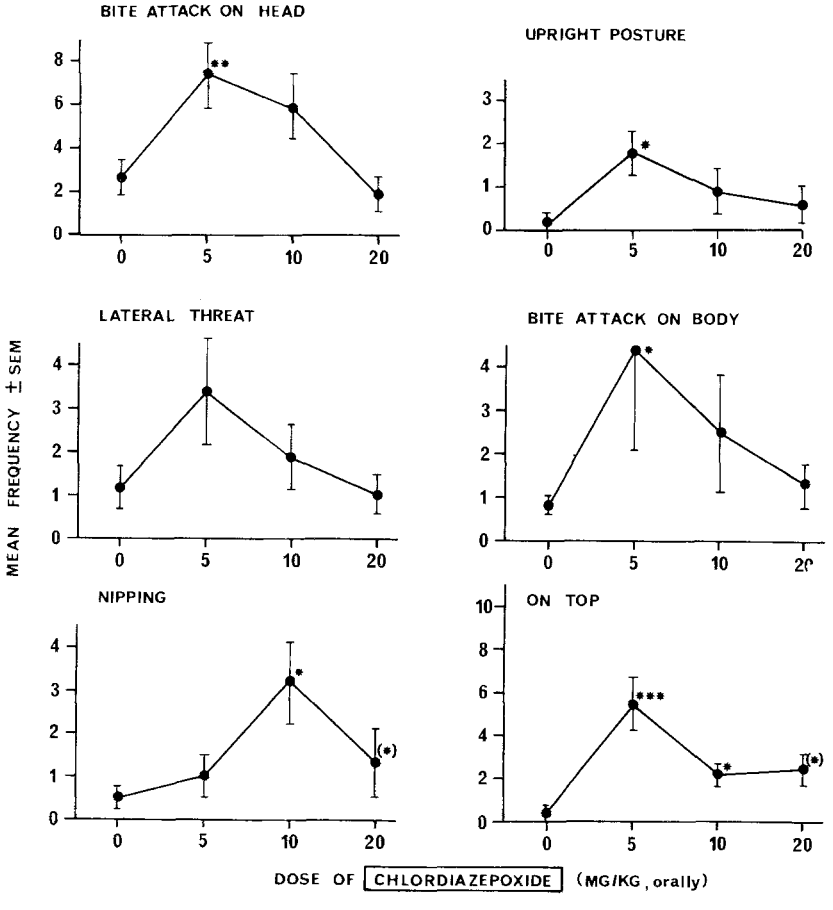

Fig. 3. Frequencies of individual aggressive elements after CDP treatment. Significant two-tailed differences from 0 mg/kg are depicted; (*) $P<0.10$; * $P<0.05$; ** $P<0.02$; *** $P<0.01$

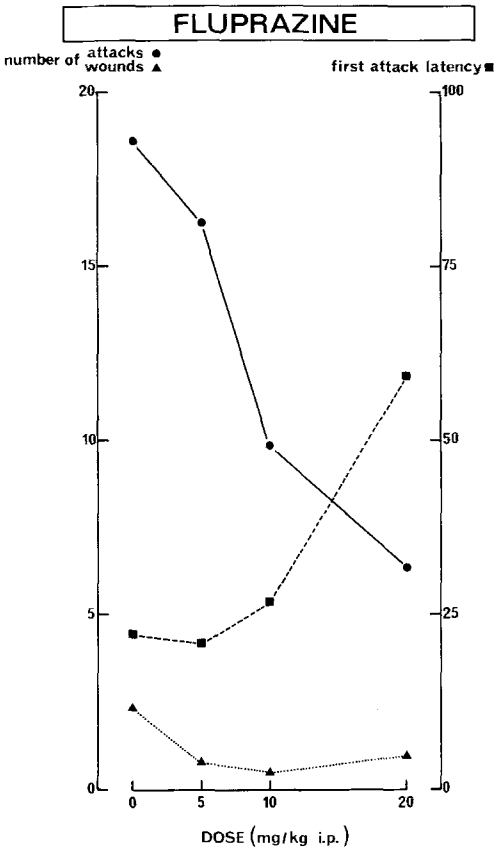

Fig. 4. Effect of fluprazine (0, 5, 10 and 20 mg/kg, IP) on the number of attacks (●), the number of wounds (▲) and the latency (s) to the first attack (■). Eight females received each dose in a randomized order 30 min before testing

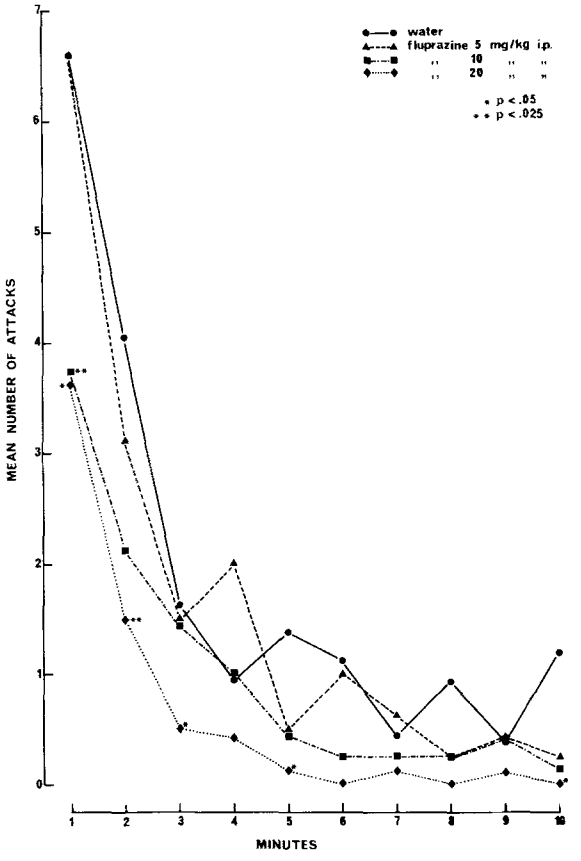

Fig. 5. Effect of different dosages of fluprazine on the distribution over time of the attacks in a 10-min maternal aggression test. Significant two-tailed differences from 0 mg/kg are depicted; * $P<0.05$; ** $P<0.02$

Table 2. Effect of fluprazine on seven behavioural categories in maternal aggression of S3 females

Behavioural categories	Dose of fluprazine (mg/kg IP)				Friedman statistic		
	0	5	10	20		*df*	*p*-value
	Mean frequency ± SEM						
Inactivity	3.9 ± 0.9	5.9 ± 1.5	10.4 ± 3.2	11.9 ± 2.4	4.95	3	0.17
Exploration	101.7 ± 8.3	94.4 ± 11.7	70.8[a] ± 14.5	53.5[b,c] ± 6.4	7.95	3	0.047
Body care	2.4 ± 0.7	3.4 ± 1.2	2.1 ± 0.7	1.8 ± 0.7	1.91	3	0.59
ISB	56.3 ± 6.9	38.0 ± 6.1	31.8[a] ± 6.6	17.6[b,d,e] ± 3.1	14.55	3	0.0017
Aggression	26.3 ± 2.5	23.6 ± 5.3	13.8[b] ± 2.2	11.3[b,c] ± 2.8	11.4	3	0.009
Avoidance	5.6 ± 0.8	2.8 ± 1.1	5.6 ± 1.5	2.5 ± 0.8	7.01	3	0.07
Pup care	1.3 ± 0.6	6.3 ± 4.1	2.3 ± 0.6	6.5 ± 2.9	4.39	3	0.22
	Mean duration (s) ± SEM						
Inactivity	32.9 ± 15.2	35.9 ± 9.2	110.5[a,c] ± 30.2	136.7[b,c] ± 26.3	12.8	3	0.0048
Exploration	309.6 ± 20.5	309.1 ± 27.9	201.6 ± 33.8	231.2 ± 46.2	4.95	3	0.17
Body care	11.9 ± 5.0	44.2 ± 19.8	29.7 ± 8.0	21.5 ± 7.0	3.0	3	0.39
ISB	188.2 ± 16.6	120.8[a] ± 23.0	95.9[b] ± 14.5	57.9[b,c,e] ± 8.6	15.0	3	0.0013
Aggression	47.9 ± 7.6	42.7 ± 11.0	18.6[b,c] ± 2.6	18.8[b] ± 6.3	11.6	3	0.0087
Avoidance	7.1 ± 0.9	3.7 ± 1.6	8.7 ± 2.7	3.5 ± 1.6	3.7	3	0.29
Pup care	3.4 ± 1.6	60.1[a] ± 20.5	135.8[a] ± 55.2	132.3[b] ± 49.7	7.46	3	0.058

[a] Significant difference from 0 mg/kg at $P<0.05$
[b] Significant difference from 0 mg/kg at $P<0.01$
[c] Significant difference from 5 mg/kg at $P<0.05$
[d] Significant difference from 5 mg/kg at $P<0.01$
[e] Significant difference from 10 mg/kg at $P<0.05$

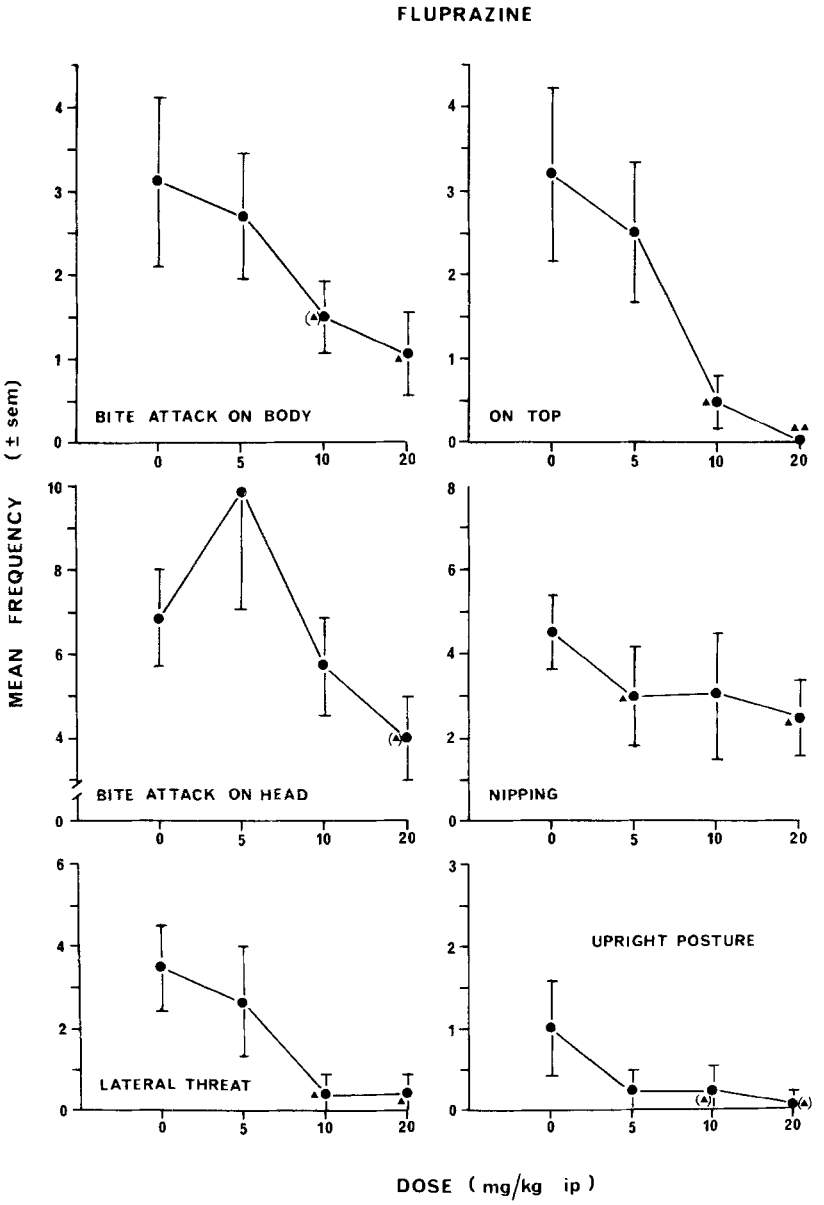

Fig. 6. Frequencies of individual aggressive elements after fluprazine treatment. Significant two-tailed differences from 0 mg/kg are depicted; (▲), $P<0.10$; ▲ $P<0.05$; ▲▲ $P<0.02$

10 mg/kg)=0, $P<0.001$; t(0 vs 20 mg/kg)=0, $P<0.01$; t(5 vs 10 mg/kg)=2, $P=0.02$; t(10 vs 20 mg/kg)=4, $P=0.05$] but not the number of wounds ($\chi^2=3.5$; df=3; $P=0.32$). The number of wounds was too low to detect any shift in preferred target areas. The effect of Flu on the latency to the first attack was of borderline significance ($\chi^2=7.3$; df=3; $P=0.06$). Figure 5 shows the distribution of attacks within a 10-min encounter 30 min after Flu treatment.

For all four treatments (vehicle, 5, 10, and 20 mg/kg IP) a significant decreasing trend was present from the 1st min on.

Moreover, Fig. 5 shows that all dosages of Flu decreased the number of attacks over time, although the 5 mg/kg dose was not significantly different from vehicle. The two highest doses of Flu (10 and 20 mg/kg) decreased in particular the number of attacks in the first 2–3 min. Later, numbers were so low that no significant effect could be seen. Table 2 shows the effects of Flu on seven behavioural categories of maternal behaviour in the 10-min encounters with male intruder rats.

Aggression (both frequency and duration) showed a dose-dependent decrease, which was also evident in ISB. Exploration (only frequency) also showed a decrease, whereas Inactivity (duration) and Pup Care increased. No effects were present in Body Care and Avoidance.

The individual agonistic elements (Fig. 6) also showed dose-dependent decreases with increasing doses of Flu, indicating the strong antiaggressive effects of this drug.

Discussion

The present data on CDP and Flu clearly show that the agonistic behaviour of lactating female rats towards male intruders can be easily manipulated by psychoactive drugs. Although maternal aggression is restricted to a certain postpartum period, which does not accommodate simple experiments, the ease with which aggression can be evoked and the rapid testing (within 5 min) are strong arguments in favour of such a female aggression model for testing psychoactive drugs. Another very attractive methodological feature of this kind of aggression is its extremely short at-

tack latency in contrast to most male aggression models (cf. Van der Poel et al. 1984a). Even naive lactating females which have never met an intruder before attack with surprisingly short latencies.

Low doses of CDP enhanced the aggressive behaviour of females directed against male intruders. Simple measures such as shortened attack latencies and increased number of attacks already suffice to demonstrate this effect. More detailed ethological analysis confirms this observation: all aggressive behavioural elements show a similar dose-effect curve.

However, more careful analysis of the total behavioural repertoire sheds some light on the mechanism by which CDP exerts its action. Pup care, as well as inactivity and body care (self-directed activities), remain at their original level. The stimulatory effect on aggression is paralleled by an increase in introductory social behaviour. The duration of ISB increases at the expense of exploration, which is reduced both in frequency and duration. CDP thus increases social behaviour, perhaps by reducing the approach-avoidance conflict always present in social interactions (Van der Poel et al. 1984a). Aggression can thus be viewed as the resultant of two opposing tendencies, namely approach and attack vs flight and defense. External and internal factors influence this balance, thereby optimizing the best chances for survival and performing the most functional behaviour at the least risks. In maternal aggression the resultant behaviour is largely determined by the strong approach tendencies, as is clear from the behaviour displayed: Initiative, piloerection, teeth chattering, jump attacks, lateral threat and bite attacks on the head and body. In contrast, defending animals perform upright postures, flight, crouching and produce 22 kHz ultrasound (Olivier et al. 1984b). Moreover, the very short attack latencies do not promote the hypothesis of fear-induced attacks. Defending rats usually only attack when no alternative flight possibilities are available, such as during cornering. This behaviour depends on the attacks of the offensive animal, and implies by nature longer latencies for the (fear or escape) motivated counter-attack. As can be seen from Table 1, Avoidance was reduced after CDP treatment, although this was not statistically significant. Thus, the proposed anticonflict action of benzodiazepines may influence the approach-avoidance conflict in a very subtle way: a minimal decrease in the already weak tendency to evade nevertheless results in a marked increase of offensive attack behaviour. After the scales have tipped in favour of offense, the attack patterns are normal; sequential and cluster analysis (unpublished observations) reveal no marked shift in the structure of agonistic behaviour. However, a more careful analysis of the approach-avoidance conflict in social interactions could be useful to analyse the mechanism of action of CDP on aggressive behaviour.

That CDP exerts its action by a direct facilitation of neural elements involved in agression is unlikely. Current thresholds for brain stimulation-induced aggression are not lowered, only the morphology of attacks changes. At higher dosages the fierce bites are more often replaced by gentle bites and skin pulling, both in male and female rats (Kruk et al.; Olivier et al. unpublished observations). Since olfactory mechanisms play a role in agonistic behaviour in rodents, an indirect effect of CDP by changing sensory processing may be of importance in the observed effects. Support for this idea is found in the increase in social interest (ISB) after CDP. However, in microsmotic species, such as man, in which olfaction is less prominent, increased aggression at low dosages of CDP has also been reported.

In male intraspecific aggression models, we (Olivier et al. 1984a; Olivier and van Dalen 1982) found contradictory results with CDP. In a social behaviour interaction model in mice and rats, CDP at lower doses enhanced aggression, as found for maternal aggression, whereas in a resident-intruder model (territorial aggression) CDP at the same doses reduced aggression in one strain (WEzob), but enhanced it in another (S3) (Van der Poel et al. 1984b). Several aggression paradigms using different species (Arnone and Dantzer 1980; Essman 1978; Gardner and Guy 1984; Miczek and Barry 1976; Miczek and Krsiak 1979, 1981; Krsiak et al. 1981, 1984) have shown that the behavioural effects of CDP and other benzodiazepines strongly depend on the external situation. Perhaps we may add that strain differences also contribute to the divergence of effects. The importance of the environmental situation and the state of the animal make a simple and direct stimulatory effect of CDP unlikely, although this cannot be ruled out. Miczek and O'Donnell (1980) have hypothesized that the facilitatory effect of CDP on aggression is possibly a rate-dependent phenomenon. The data on CDP and fluprazine in this paper may indeed suggest that baseline differences between both experiments may have influenced the results. Unpublished work both on CDP and Flu, however, has shown that CDP (and Flu) retain the same action when tested in animals with varying baseline levels of aggression, suggesting that the behavioural effects are not dependent on rate-dependency phenomena. A very remarkable point which seems dissociated from the aggression effect was the increased feeding observed after CDP treatment. Although this phenomenon has been observed in specific feeding experiments (Cooper 1983), we did not expect this in a typical agonistic test situation.

Flu, a potent antiaggressive drug (Benton et al. 1983; Bradford et al. 1984; Olivier and van Dalen 1982; Olivier et al. 1984a, b) had clear antiaggressive effects in this female aggression model. However, it differed in the profile of action as described in male aggression: a decrease in aggression leaving social interaction largely intact and no sedative aspects (Olivier et al. 1984b). Flu, in this female paradigm, increased inactivity.

The enhanced inactivity observed, especially after 10 and 20 mg/kg is largely spent on sitting (lying is not enhanced), during which the female watches the intruder. The place where sitting is performed is mostly between the intruder and the nest, because most intruders, after the first attacks (which are still performed by Flu-treated females) try to evade as much as possible the females' nesting place.

In any event, it is evident that by reducing aggression, as Flu certainly does, the protection and care for the young does not suffer, but rather seems enhanced. The females used an alternative strategy to defend the pups by physically preventing the intruder from approaching the nest (pup care = on nest).

The maintenance of pup care even at reduced aggression levels suggests that Flu does not induce its antiaggressive effects by nonspecific actions, but keeps a rather unique profile in this model. However, as long as other putative antiaggressive agents are not tested it is difficult to predict how specific the effects of serenics are in this female model. Preliminary data on haloperidol, a neuroleptic with antiag-

gressive properties, shows that this compound has antiaggressive actions in maternal aggression, but does this in a quite different and more sedative way from Flu. In maternal aggression experiments in mice (Ieni 1983) haloperidol (1–2 mg/kg) decreased maternal aggression but at the same time decreased locomotory activity similarly, also indicating the non-specific antiaggressive effect of haloperidol. We (Olivier and van Dalen 1982; Olivier et al. 1984a) and others (cf. Miczek and De Bold 1983) have confirmed this nonspecific effect of haloperidol in male aggression models in several species.

Other serenic drugs tested in our laboratory (e.g. DU 28412 – Bradford et al. 1984) show a similar behavioural profile to fluprazine, both in this female as in several male aggression models. Further studies of drug effects in maternal aggression will possibly elucidate what the specific properties of this female model are. The unique hormonal status of lactating females (high prolactin levels) is certainly different from male aggression models used, whereas stimuli necessary to initiate maternal aggression (e.g. suckling) do not play a role in male aggression.

Despite the fundamental differences in male and female (maternal) aggression, the data obtained so far on fluprazine, chlordiazepoxide and DU 28412 and (unpublished) on haloperidol, *d*-amphetamine and naloxone do not point to different processes in the control of aggressive behaviour in males and females.

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