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# Changes in the Structure of the Agonistic Behavior of Mice Produced by D-Amphetamine

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MORO, M., A. SALVADOR AND V. M. SIMÓN. *Changes in the structure of agonistic behavior of mice produced by D-amphetamine.* PHARMACOL BIOCHEM BEHAV **56**(1) 47–54, 1997.—The effects of three acute doses of D-amphetamine (0.25, 1.5 and 3 mg/kg) were studied in a model of isolation-induced aggression in male mice. An ethopharmacological analysis of the encounters was carried out, which studied the frequency, total and mean duration of different behavioral categories, including the temporal distribution of attacks and the duration of inter-attack intervals. The results show a reduction in the total and mean duration of the Attack category and an increase in motor activity manifested by longer durations, both total and mean, of Non Social Exploration and shorter Immobility. The temporal analysis of Attack revealed an increase in the number of very short (<15 s) inter-attack intervals and a temporal redistribution of the attacks to later in the course of the social encounters. These results confirm for a complex behavior such as aggression, that D-amphetamine, even at low doses, favors a fragmentation and repetition of motor routines with a simultaneous reduction in the influence of environmental cues on the control of behavior. 

D-amphetamine Aggression Ethopharmacology Mice

AMPHETAMINE has been considered to be a predominantly antiaggressive substance in a dose range of 0.25-10 mg/kg, enhancing flight behavior and decreasing attacks and threats (22). At doses greater than 10 mg/kg, thought of as toxic, amphetamine-treated animals show what has been called "amphetamine aggressiveness or rage" that is characterized by fragmented agonistic acts and postures embedded in stereotyped motor routines (25). However, the effects of amphetamine on agonistic behavior are more complex depending on variables such as species, previous behavioral experience, social status, stimulus situation, experimental model and, most important, dosage (19,29).

In fact, contradictory effects of low doses of amphetamine on aggressive behavior have been found. For instance, D-amphetamine decreased maternal agonistic behavior of rats (number of attacks) at 0.5, 1 and 2 mg/kg but did not affect the attack latency (30). In other models, such as isolation-induced aggression in mice, and with a dose of 1 mg/kg a reduced frequency of attacks without an alteration in locomotor activities has been reported (11). Nevertheless, in other studies, D-amphetamine tended to increase the frequency of fights in mice with doses of 0.5, 1, 2 and 4 mg/kg (8) and the frequency of attack bites and sideways threats (0.3 and 1 mg/kg) (20). Using the intruder-resident model, increases in attack frequencies in mice have been reported in a dose range of 0.3–3 mg/kg (38). Furthermore, the appearance of motor stereotypies at doses lower than 10 mg/kg has been described. These stereotypies are clearly registered at doses such as 6 mg/kg (1) and at 4 mg/kg the motor activity of the treated animals was interfered with and resulted in a decrease of the global level of activity in comparison to animals treated with lower doses (1 and 2 mg/kg) (18). Taking this into account, a partition can be made in the range of 0.25–10 mg/kg, to differentiate between doses that do not provoke stereotypies and have unclear effects on aggressive behavior (lower than 4 mg/kg), and intermediate to high doses (higher than 4 mg/

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kg) which produce clear antiaggressive effects and a significant increase in stereotypies and/or locomotor activity.

A valid experimental model has been an acknowledged need in the study of drug action on aggression. The ethological approach has produced biologically valid test situations and detailed behavioral measurements in an effort to gain insight into causative and functional determinants of aggressive, defensive, submissive, and flight behaviors (25). This approach facilitates the determination of the effects of drug treatment on a wide behavioral repertoire that takes place in a social encounter between members of the same species (2,5), which is especially important in the research into amphetamine effects since an increase in motor behaviors and stereotypies may compete with other behaviors (15,19). Incompatibility between behaviors has been asserted as the explanation of the antiaggresssive effects of D-amphetamine, for example, an increased level of general motor activity in amphetamine-treated animals has been suggested as the cause of increased flight reactions (22). The importance of studying other behaviors is evident considering that aggression takes place in a social situation where other than agonistic behaviors are produced. In fact, substantial reductions in a variety of social and agonistic behaviors shown by intruder rats, including pinning, boxing, chasing, face offs, side threats, crawling under other rats, and mounting have been found at a dose of 4 mg/kg (36). These effects on non-aggressive social behaviors are especially important in studies on pharmacological models of the negative symptoms of schizophrenia.

The majority of the studies on aggressive behavior mentioned above have analyzed single behavioral measures, generally frequency, but in order to understand the effects of drugs on complex behaviors, it would be necessary to assess behavioral responses in a more accurate way, for example, by recording more than one measure (latency, total and mean duration and frequency) (1). Additionally, the study of sequences of concrete behavioral categories and the analysis of temporal patterns of behavioral elements could contribute to deepen our knowledge of the effects of psychoactive compounds on behavior (2,24). It is possible to study elements of behavior in the temporal context in which they occur, reflecting the fact that social and agonistic interactions are complex patterns of behavioral elements, and if only measures of a single component are studied important information could be lost (25,26). To cite an example in rats, the behavioral elements of pursuit, threat, attack bite and aggressive posture can be identified to occur, (a) as part of a sequence with one element following the next with high probability; and (b) as part of an epoch or burst of aggressive behavior that alternates with periods of relative behavioral quiescence (25). Studying the effects of amphetamine by means of these methods provides evidence of modifications in the structure of attack behavior (transitions between behavioral categories and their temporal patterns). Thus, with low doses of the drug significant changes in the pattern of behaviors have been found although this is not the case when single measures (total duration or frequency) are registered (12,21). The usefulness of a detailed analysis is illustrated in studies concerned with the effects of amphetamine in other complex behaviors (3,33,36).

Taking all this into account, an experiment was designed to study the acute effects of D-amphetamine on aggression, using the doses that have provoked contradictory results, but below the minimal doses that have produced stereotypies to avoid incompatibility between behaviors. Moreover, the effects of D-amphetamine on the different behaviors shown by mice in a social encounter have been studied using an ethopharmacological based behavioral evaluation system, including agonistic, social and motor behaviors. Finally, a detailed analysis of the behavioral data to study the effects of the drug on the behavioral structure and patterns of attack behavior was carried out. Our analysis involved, not only commonly used parameters such as frequency, total and mean duration, but others that were more specific such as first-order transitions, inter-attack intervals and temporal distribution of offensive behaviors.

## METHODS

### *Subjects*

Fifty-two OF1 male mice, from Iffa Credo (France), aged 42 days, were individually housed for 6 weeks in plastic cages ($24 \times 13 \times 14$ cm) and used as experimental and control subjects. A further 54 animals were housed in groups of 9 in larger cages ($28 \times 28 \times 14$ cm) and used as "standard opponents," after being rendered temporally anosmic by intranasal lavage with a 4 % zinc sulphate solution a day before testing (see 35). Mice were fed food and water ad lib and subjected to a 12-h light-dark cycle (lights on 10:00–22:00 h local time). Laboratory temperature was kept at $20 \pm 2$°C. Subjects were weighed once a week.

### *Drug Administration*

Three groups of animals ($n = 13$) were injected i.p. with 0.25, 1.5 or 3 mg/kg of D-amphetamine sulphate (courtesy of Smith Kline & French, Great Britain), respectively and one group ($n = 13$) with 5 ml/kg physiological saline (control group) 30 min before the behavioral test.

### *Social Encounter Test*

Encounters lasting 10 min between an isolated mouse and an anosmic opponent in a neutral area ($60 \times 40 \times 20$ transparent glass cage), illuminated by a white light (60 watts) were carried out. This was preceded by a minute of adaptation in which the animals were separated by a plastic partition. Encounters (in which each animal participated only once) took place starting in the second hour of the subjects' dark period and were recorded with a video camera positioned in front of the test cage.

Anosmic grouped mice were employed as "standard" opponents because they elicit attack but never initiate such behavior (4). On some rare ocasions, anosmic animals show aggressive behaviors, presumably due to a failure in the anosmic procedure; in these cases, the tests are interrupted and suppressed in posterior analyses.

### *Behavioral Analysis*

The behavior of experimental animals was assessed using an ethological technique based on a computerized observational procedure (5). The behaviors are classified in 11 broad categories. Each category included a variety of different behavioral postures and elements. The categories and their constituent elements are as follows:

1. body care (abbreviated groom, self-groom, wash, shake, scratch);
2. digging (dig, kick dig, push dig);
3. nonsocial exploration (explore, rear, supported rear, scan);

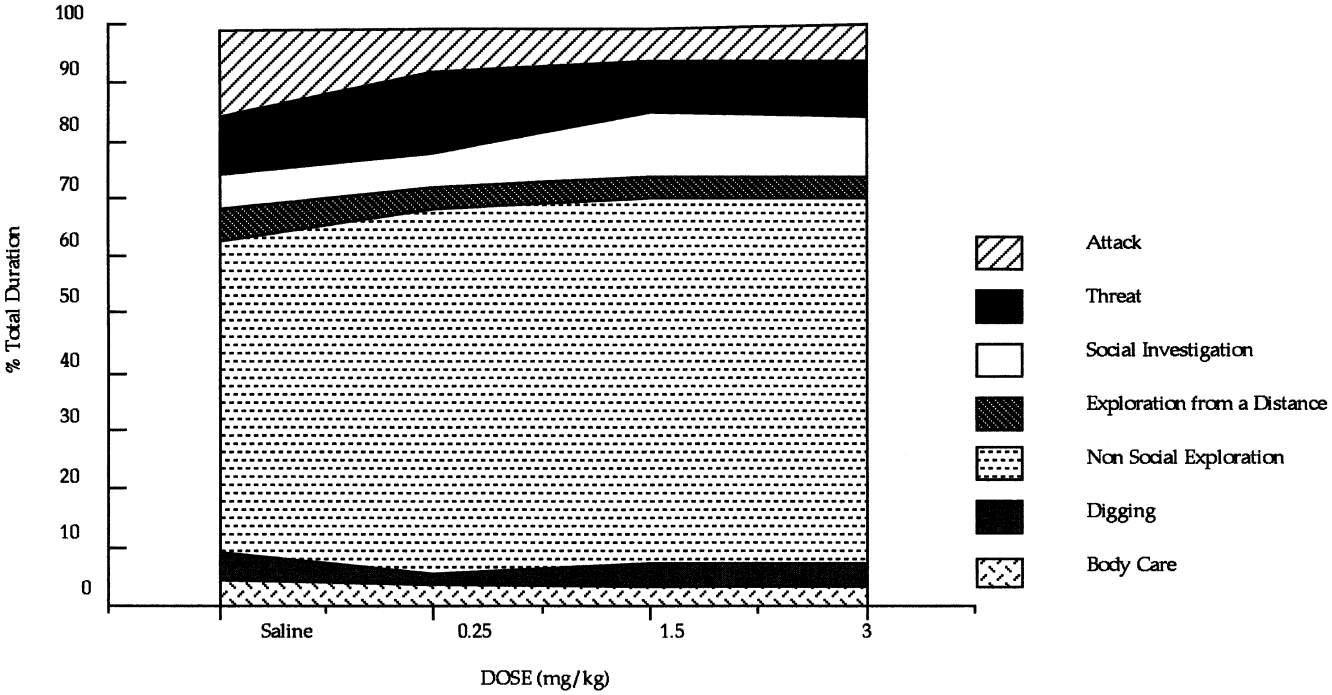


FIG. 1. Percentage of total duration of all behavioral categories.

4. exploration from a distance (approach, attend, circle, head orient, stretched attention);
5. social investigation (crawl over, crawl under, follow, groom, head groom, investigate, nose sniff, sniff, push past, walk around);
6. threat (aggressive groom, sideways offensive, upright offensive, tail rattle);
7. attack (charge, lunge, attack, chase);
8. avoidance/flee (evade, flinch, retreat, ricochet, wheel, startle, jump, leave, wall clutch);
9. defensive/submissive (upright defensive, upright submissive, sideways defensive);
10. sexual behavior (attempted mount, mount);
11. immobility (squat, cringe).

A detailed description of all elements can be found in Brain et al. (5) and Martinez et al. (17). The analysis of the videotapes involved assessment only of the behavior of the experimental and control animals. This analysis was performed by a trained observer who was blind to the experimental group to which each animal belonged.

The computer program gives information of total duration (accumulated time spent in each category), frequencies (number of occurrences of each category in the 10 min test), mean duration (total duration divided by the frequency of each category) and the number of transitions between pairs of categories. Finally, it provides the sequence in which the different categories have been observed and registered, and the duration of each occurrence. From these data, the latency of each category, the duration of the intervals between consecutive appearances of the same category, and the relative frequencies (number of times that a given category appears in limited temporal periods) can be calculated.

No sexual behavior was recorded, so this category does not appear in the results.

*Statistical Analysis*

Kruskal-Wallis tests were carried out to assess the variance in total duration, frequency, mean duration and first-order transitions over different doses in the behavioral categories. The comparisons between groups were performed by the Mann-Whitney U-test. The analyses were performed using nonparametric statistics since the criteria for parametric statistics (ANOVA) were not met by the data.

Several additional parameters were calculated for the Attack category, namely: latency, number of inter-attack intervals of each duration, and frequency of attacks over time (60 s). To compare latencies, Kruskal-Wallis and Mann-Whitney U-tests were performed. The comparisons between the number of attacks in each minute and the number of transitions in the control group and each of the treated groups were analyzed by the Student's *t*-test. The differences in duration of inter-attack intervals and the number of attacks in each minute were estimated by the chi-square test.

## RESULTS

*Analysis of all Behavioral Categories*

The medians and ranges of the total duration, frequency and mean duration of the behavioral categories which reached statistical significance are shown in Table 1.

*Total duration.* Total duration of Attack was decreased in the D-amphetamine-treated groups although it was only statistically significant with the two higher doses. Total duration of Threat was unaffected in these groups but was increased in the lowest dose (see Fig. 1). Treated groups spent more time in Non Social Exploration and less in Immobility in comparison to controls.

*Frequency.* Statistically significant changes in the frequency of different behavioral categories appeared only in Immobility

which showed a decrease. However, important increases in the number of occurrences of different categories, including Non-Social Exploration and Social Investigation must be noted. Also, an increase in the number of offensive behaviors (Threat and Attack) appeared with the lowest (0.25 mg/kg) dose. The number of transitions from one behavior to another was increased in all the D-amphetamine treated groups (208.46, 187, 199.46) but the differences were only statistically significant when comparing control group (175.76) with the group treated with the low dose ($t = -2..25$; $p<0.05$). Nevertheless, the ratio attack/total number of behaviors was not significantly different among the four groups, although an increase in the low dose was evident (0.10 in the 0.25 group vs 0.07 in the control, and 0.069 and 0.061 in the intermediate and high doses, respectively).

*Mean duration.* Mean duration of the behavioral categories was calculated in order to consider the total duration and the frequency simultaneously. Our results showed that the mean duration of Attack, Exploration from a Distance and Immobility were significantly reduced in D-amphetamine treated mice when compared with controls (see Table 1).

*First-order transitions.* Differences between treated groups and controls in the number of first-order transitions (dyads of two behavioral categories) were calculated using the Mann-Whitney U-test. Moreover, for each category, the probabilities of being preceded by all the other categories were calculated in the following way: for each group, the mean of the occurrence of a given dyad was calculated and was divided by the mean of the total of dyads registered. The probabilities of dyads related with the significant transitions are presented in Table 2.

In the animals treated with the lowest dose, the transitions Threat-Non Social Exploration (U = 131.5/37.5; $p<0.02$) and Non Social Exploration-Threat (U = 133/36; $p<0.02$) were significantly more frequent than in the controls. The close examination of the precedent behaviors of both categories showed an increased probability of the temporal contiguity of these categories in the treated animals ($p = 0.29$ for the first transition and $p = 0.35$ for the second) in comparison with the control ($p = 0.15$ and $p = 0.28$, respectively). In the control group the behavior with more probability of being the precedent of Threat was Social Investigation ($p = 0.37$), followed by Non Social Exploration ($p = 0.26$). This pattern was changed in the animals treated with 0.25 mg/kg of D-amphetamine, where the more probable precedent behavior of Threat was Non Social Exploration ($p = 0.35$). On the other hand, when Non Social Exploration was considered as a consequent, five behavioral categories with similar probabilites ($p = 0.12$ to $p = 0.17$) of being precedents of this category were observed in the control group but in the group treated with 0.25 mg/kg of D-amphetamine Threat was clearly the more probable precedent ($p = 0.29$). The higher frequency of the transitions Threat-Non Social Exploration and vice-versa is not only explained by the higher occurrence of Threat in the low dose group, but also by a change in the global structure of the rest of the behavioral categories in relation with Threat and Non Social Exploration.

In the 1.5 mg/kg group (U = 115.5/40.5; $p<0.05$) and in the 3 mg/kg group (U = 132/37; $p<0.02$), the transition Non Social Exploration-Social Investigation was significantly more frequent than in the control group. Simultaneously to this, a reduction in the probability of the Exploration from a Distance as antecedent of Social Investigation was found (see Table 2). A change in the structure of behavior was observed showing

TABLE 1

MEDIANS AND RANGES FOR TOTAL DURATION IN SECONDS (TD), FREQUENCY (F) AND MEAN DURATION (MD) OF BEHAVIORAL CATEGORIES

| | | DOSES (mg/kg) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Saline | | 0.25 | | 1.5 | | 3 | |
| Categories | | Median | Range | Median | Range | Median | Range | Median | Range |
| Non social exploration + | TD | 318.7 | 237–273 | 354.7** | 275.9–429.6 | 382.1*** | 303.33–410.8 | 373.7* | 280–465.3 |
| | F | 59 | 53–97 | 68 | 43–102 | 66.5 | 49–98 | 74 | 53–96 |
| | MD | 5.4 | 3.3–6 | 4.5 | 3.3–8.6 | 5.1 | 3.5–7.6 | 4.5 | 3.7–8.3 |
| Exploration from a distance + | TD | 33.9 | 8.8–88.2 | 22.5 | 2.2–45.1 | 21.6 | 7–50.5 | 24.1 | 4.1–44.7 |
| | F | 21 | 9–37 | 16 | 4–47 | 18 | 7–36 | 21 | 5–34 |
| | MD | 1.5 | 0.9–2.9 | 0.9*** | 0.6–1.9 | 1.2 | 0.6–1.9 | 1.2* | 0.16–1.6 |
| Attack + | TD | 89.9 | 4.7–117.2 | 41.8 | 13.2–96.7 | 32.9* | 2.7–102.4 | 35.6** | 0–77 |
| | F | 13 | 2–18 | 23 | 5–50 | 12.5 | 3–33 | 12 | 0–34 |
| | MD | 6.1 | 2.4–16.7 | 2*** | 1.4–3.4 | 2.8*** | 0.9–4.1 | 2.9*** | 0–11.1 |
| Immobility + | TD | 6 | 0.2–124.7 | 1.2 | 0.02–17.2 | 21 | 0–11.7 | 0.4 | 0–26.4 |
| | F | 5 | 1–30 | 2 | 1–7 | 2* | 1–7 | 1*** | 1–12 |
| | MD | 1.1 | 0.2–4.2 | 0.5* | 0–2.5 | 0.5* | 0–2.1 | 0.4** | 0–1.8 |

+ shows significant variation on the Kruskal-Wallis test $p < 0.05$; *** differs from control $p < 0.01$ on Mann-Whitney *U* Test; ** differs from control $p < 0.02$ on Mann-Whitney *U* Test; * differs from control $p < 0.05$ on Mann-Whitney *U* Test.

TABLE 2

PROBABILITIES OF TRANSITIONS BETWEEN CATEGORIES

| Categories | | Dose of D-Amphetamine mg/kg | | | |
|---|---|---|---|---|---|
| Precedents | Consequents | Saline | 0.25 | 1.5 | 3 |
| Body care | Non Social Exploration | 0,13 | 0,13 | 0,14 | 0,14 |
| Digging | Non Social Exploration | 0,17 | 0,09 | 0,18 | 0,15 |
| Exploration from a distance | Non Social Exploration | 0,15 | 0,13 | 0,13 | 0,13 |
| Social investigation | Non Social Exploration | 0,18 | 0,16 | 0,22 | 0,23 |
| Threat | Non Social Exploration | 0,15 | 0,29 | 0,18 | 0,19 |
| Attack | Non Social Exploration | 0,09 | 0,13 | 0,09 | 0,10 |
| Immobility | Non Social Exploration | 0,10 | 0,04 | 0,04 | 0,04 |
| Non social exploration | Social Investigation | 0,59 | 0,70 | 0,66 | 0,68 |
| Exploration from a distance | Social Investigation | 0,31 | 0,19 | 0,23 | 0,21 |
| Non social exploration | Threat | 0,26 | 0,35 | 0,24 | 0,30 |
| Exploration from a distance | Threat | 0,15 | 0,15 | 0,13 | 0,15 |
| Social investigation | Threat | 0,37 | 0,23 | 0,39 | 0,38 |
| Attack | Threat | 0,21 | 0,25 | 0,22 | 0,16 |

that the amphetamine treated animals approached the opponent more directly than controls.

*Microanalysis of the Attack Category.*

*Latency to first attack.* The latencies in the groups treated with D-amphetamine (medians of 107.3, 126.6 and 79.7 s for the 0.25, 1.5 and 3 mg/kg doses, respectively) were higher than in the control group (48.9 s), however, no significant differences were evident in the Kruskal-Wallis test.

*Intervals between attacks.* The intervals have been scaled according to their duration. A chi-square test was performed to compare the number of intervals of each duration shown in the different groups. There was a significantly higher number of very short intervals, i. e. shorter than 15 s in the treated animals in comparison with controls. Fig. 2 shows the percentage of intervals shorter than 15 s As can be seen, the increases appeared in the very short intervals (<5 s).

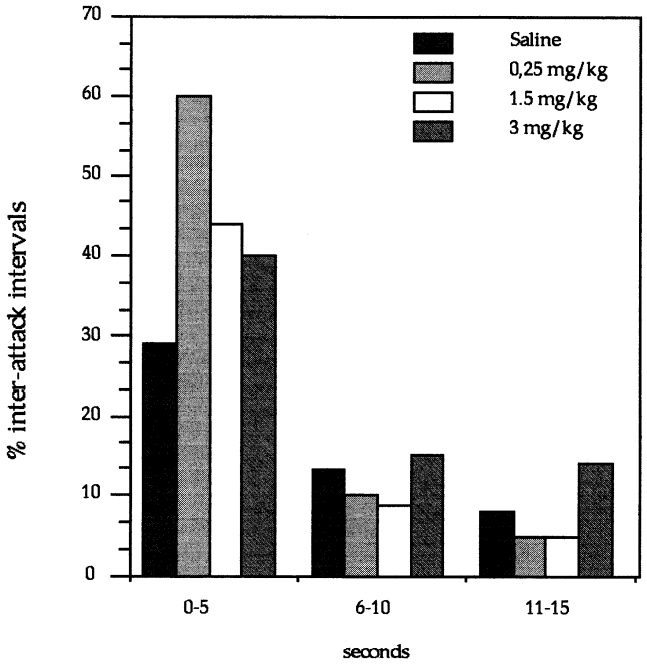


FIG. 2. Percentages of inter-attack intervals shorter than 15 s, in the four experimental groups.

As a complement of the temporal evolution of the attacks, the duration of the successive inter-attack intervals was estimated and is represented in s in order of appearance in Fig. 3.

*Temporal evolution of attacks.* The number of attacks in periods of 60 s was calculated, and comparisons between each of the treated groups and control were made by the Chi-square test. As can be seen in Fig. 4, the attacks of the control animals were the first to consistently tail off along time in comparison with those of the treated groups. The differences between the groups treated with 0.25 and 3 mg/kg of D-amphetamine and the controls were statistically significant ($p<0.05$).

## DISCUSSION

Our results, using a range of low doses (from 0.25 to 3 mg/kg) and a model of isolation-induced aggression, give support to the antiaggressive effect of D-amphetamine which has been described with doses ranging from 0.25 mg/kg to 5 mg/kg and using the frequency of attacks as measurement (13,14). However, this effect has been evident in the consistent reduction in the mean and total duration of the category of Attack, whereas the frequency and the latency of Attack and all the measures of Threat were not significantly changed. Nevertheless, in the group treated with the lowest dose (0.25 mg/kg), the number of attacks and threats increased, although non significantly, and the probability of transitions from Non Social Exploration to Threat and vice-versa was significantly increased, while the probability of other dyads was reduced. Previously, it has also been reported that selected single low doses of amphetamine may occasionally increase aggressive behavior in isolated mice (19).

The stimulant effects of amphetamine on motor activity may be observed in different behaviors. Clear increases have been seen in exploratory behaviors, namely in Non Social Exploration and Social Investigation, whereas there was a reduction in Exploration from a Distance. Specifically, there was a significant increase in time spent in Non Social Explora-

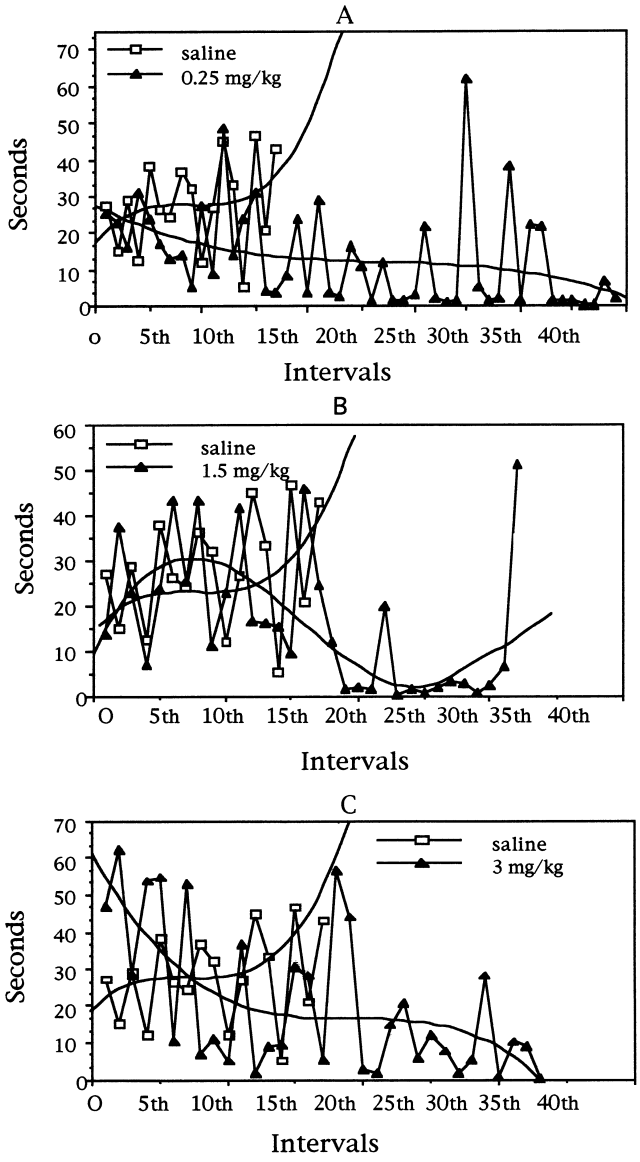


FIG. 3. Means of duration of successive inter-attack intervals in order of appearance. The data of each dose have been separately plotted against those of the saline group (3A, 3B and 3C).

tion, a result generally consistent with the literature (30,31). Probably, the motor stimulant effects of amphetamine were also responsible for the significant differences between D-amphetamine treated animals and controls in transitions including Non Social Exploration but not in the transitions involving Attack. Parallelly to these increases of motor activity, a significant drug-induced decrease of duration, mean duration and frequency of the category of Immobility was observed. Moreover, stereotypies were not evident and neither was there an increase in categories such as Care of Body Surface or Digging, which have been considered as easily affected by stereotypes (10,15). These results agree with the literature (1,6) in the sense that relatively low doses of amphetamine appear to produce locomotor-activating effects (by acting on the mesolimbic DA system) whereas higher doses produce stereotypies (mainly affecting the nigrostriatal system).

In this experiment the measure that shows the antiaggressive effect most clearly was the mean duration of Attack. According to these results, amphetamine diminishes the duration of Attack but does not inhibit its initiation nor reduce its number. Thus, the D-amphetamine treated animals show shorter attacks than controls (3,31). Moreover, amphetamine treatment increases the number of short inter-attack intervals (<15 s) whereas it decreases the number of longer ones (>15 s) which partially supports previous findings (21). Examining these short intervals more closely, it becomes evident that their increase is due to a higher number of the very short ones, i. e. those shorter than 5 s This prevalence of very short intervals, which is particularly apparent in the 0.25 mg/kg dose, suggests the existence of a fragmented sequence of aggressive episodes without significantly altering the order of appearance of successive behaviors in comparison with controls.

Taking into account the duration of successive inter-attack intervals along time, there were clear differences between controls and D-amphetamine treated mice. While the inter-attack intervals of the controls rapidly became longer as the session progressed, those of the treated animals grew shorter and attacks were more frequent. Moreover, the analysis of the distribution of attacks along the test period shows that control animals concentrated the majority of attacks in the first 5 min of the encounter whereas treated animals showed a different pattern characterized by displacing the attacks towards the end of the social confrontation. This change was more noticeable with the low dose (0.25 mg/kg.) in which the number of attacks in the second half of the encounter was clearly higher than in the first. It has previously been reported that D-amphetamine attenuated the decline of attacks and sideways threats that are normally observed during repeated confrontations (38).

The pattern of agonistic behavior shown by treated animals, characterized by shorter attacks that persist longer in the encounter period, suggests that their aggressive behavior is disrupted. These changes are in aggreement with the general statement formulated by Lyon and Robbins that "a shift occurs to a progressively disorganized and fragmented behavior" (16). In the present results, offensive behavior was affected by low doses in such a way that only the duration of direct aggression (i.e. attack) was decreased, the episodes of aggression being interrupted (shorter mean duration of Attack) and reinitiated (shorter inter-attack intervals) at a time when submissive environmental clues normally halt this behavior. This could be considered as a disadaptative response to the environment, characterized by a predominance of fragmented motor acts (attacks) but also by a minor behavioral flexibility and sensibility to the context cues.

Some changes in social interaction observed in monkeys (7,27) under amphetamine treatment have been interpreted as a reflection of the animals developing what could be taken as a paranoic attitude towards conspecifics which is considered to be the consequence of a distortion in perception (7,28). The displacement of attacks to the second part of the behavioral test observed in our experiment could be explained by this mechanism. Usually, animals adapt their behavior to the social context so that when confronting a submissive animal (such as the anosmic opponent) they mainly fight during the first minutes until the social status is established, afterwards the number of attacks decreases and other behaviors become apparent. However, D-amphetamine treated animals would show less sensitivity to the submissive displays of the opponent and consequently would continue attacking. Nevertheless, other aspects involved in this interpretation such as increases

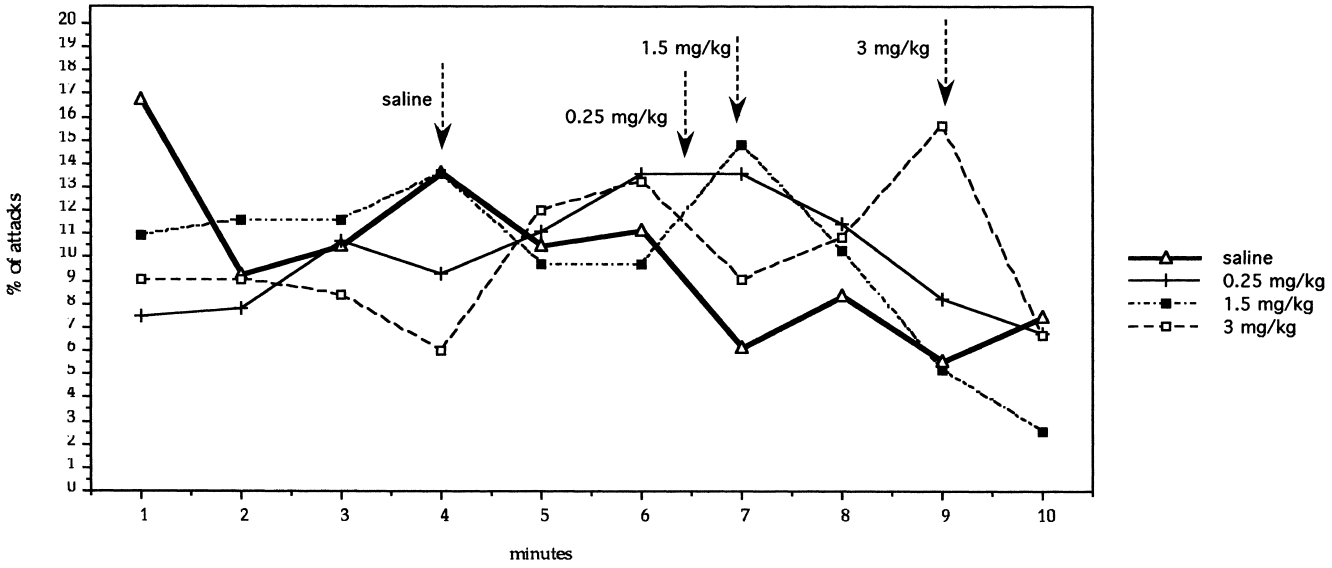


FIG. 4. Temporal distribution of attacks in the four experimental groups.

in avoidance and defense behaviors were not evident in the present study, maybe because the use of anosmic opponents did not favor these categories. Additionally, in the above cited experiments chronic treatment (7,27) or higher doses (28) were used. In general, defensive and escape reactions are less sensitive to drug action than attack behavior (23).

There has been a claim that a single behavioral measure, such as duration or frequency, is not sufficient and, therefore, it seems adequate to use different measures simultaneously to obtain a more complete knowledge of the behavioral effects of drugs. Moreover, the use of a detailed analysis of the temporal characteristics of attack behavior may shed some light on the changes in the structure of aggressive behavior brought about by amphetamine. In this study, both methodological improvements have been applied and the results demonstrate that animals under low doses of D-amphetamine show shorter attacks and inter-attack intervals than controls, although frequency remains basically the same. Another interesting modification induced by the drug refers to the timing of the attacks in the social encounter, in the sense that D-amphetamine displaces their occurrence to a later phase of the period. On the whole, with regard to aggression our results confirm a fragmentation of motor routines with a simultaneous reduction in the influence of environmental cues on the control of behavior (34), which corroborate and extend earlier findings about the complex effects that D-amphetamine has on social interaction.

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