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Comparative Study of the Behavioral Changes Evoked by d-Amphetamine and Apomorphine in Adult Cats. Dose-Response Relationship

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MOTLES, E., I. MARTINEZ, E. CONCHA, B. MEJIAS AND P. TORRES. *Comparative study of the behavioral changes evoked by d-amphetamine and apomorphine in adult cats. Dose-response relationship.* PHARMACOL BIOCHEM BEHAV **33**(1) 115–121, 1989.—The behavioral effects of d-amphetamine and apomorphine administration were studied in 17 adult cats. The doses of amphetamine administered were 0.1, 0.5, 1.0 and 5.0 mg/kg; those of apomorphine, 0.1, 0.5, 1.0 and 2.0 mg/kg. These two drugs evoked in the same animal marked differences in behavioral responses. Amphetamine induced a dose-dependent hypomotility, which was marked with the higher doses. In addition, rhythmic, bilateral slow movements of the head as a mode of stereotypy, indifference to the environment and dose-dependent increase in respiratory rate. Apomorphine elicited limb flicking, dose-dependent hypermotility and increase in olfactory behavior, the last two reactions with stereotypy characteristics. The animals appeared as if being scared, hyperreacting to sudden stimuli and showing total indifference to the surrounding environment. There were marked differences in behavioral responses evoked by these two agonists of the catecholaminergic system. These data do not conform with the behavioral reactions reported in the rat by other investigators. The disagreement with other communications is probably due to differences in reactivity of the species employed. The processes involved in the diversity of the behavioral responses of the cat to the administration of amphetamine and apomorphine have not been delucidated.

d-Amphetamine Apomorphine Behavior Dose-response relationship Cat

THE effects of several agonists and antagonists of the catecholaminergic system have been extensively analyzed in experimental animals. These studies have been carried out to clarify numerous problems related to receptors, neurotransmitters, behavior, circuitry and clinical utilities. In fact, one of the components of this system, dopamine (DA), has been implicated in the mechanism of production of Parkinson's disease (21), schizophrenia (11,17), and in the mechanisms of action of neuroleptic drugs (11, 12, 29, 31).

It is well known that amphetamine and apomorphine are catecholaminergic agonists commonly used in the laboratory. Both drugs have been administered to animals of several species (rats, mice, pigeons, guinea pigs, cats and monkeys). We became interested in these two drugs after it was found that they can unmask asymmetries between the two cerebral hemispheres when a strucutre related to turning behavior of one hemisphere has been lesioned (25). Three aspects of these data came to our attention: 1) the great variability of doses employed by different authors; 2) the scarcity of data reported on cats as compared with the amount of information from rats; and 3) the discrepancies between the behaviors we observed and those reported by other authors. In the present study we analyzed the behavior evoked in cats in which progressive doses of amphetamine and apomorphine were administered. The results attained showed that there is a dose-response relationship for most of the evoked behavioral responses. Furthermore, we observed that these two drugs induced different behavior in the same animal, and the reactions appeared different from those observed by others, especially in the rat.

METHOD

Seventeen adult cats of both sexes, weighing between 2.5–4.0 kg, were employed. Observation of the cat behavior was conducted in an open field of 3 m long by 3.0 m wide, where only a table and two chairs were present. The cats were accustomed to this enclosure previous to drug administration. Two persons were present in the sessions recording the behavior. For amphetamine, the following doses were administered: 0.1, 0.5, 1.0 and 5.0 mg/kg, and for apomorphine: 0.1, 0.5, 1.0 and 2.0 mg/kg. The doses were selected according to the literature. Apomorphine was not administered in higher doses because in previous experiments we observed, with a 2.0 mg/kg dose, intense psychomotor effects.

All doses were dissolved in a fixed volume of NaCl 0.9% (2 ml), prepared immediately before their administration. The same volume of solvent was injected as control. The drugs were given SC and each cat received only 2 injections per week. Each animal received a series of progressive doses of one of the drugs, and then, a series of the other drug. In 4 cats the administration of the drugs started with the highest dose. The complete study of each cat lasted approximately 30 days.

Before administration of the drug, the cat was observed in the selected open field; its motor activity and the relations of the animal with the observers and the environment were recorded.

After drug injection, the cat was observed continuously, and its behavior recorded every min, until a clear return to the control situation appeared. This meant an observation period of 60 to 90 min for apomorphine, and from 60 to 150 min for amphetamine. The shortest period of observation took place for the lower doses and vice versa.

There are three behaviors we think important to define: 1) normal behavior: the cat is alert, friendly and seeks to be caressed; it explores the environment, and interacts with it without fear; 2) indifferent behavior: characterized by the fact that the cat does not show any interest in the persons, or objects present in the room; 3) anxiety or fear behavior: the animal changes frequently its position and moves the head rapidly in all directions; it hyperreacts to any stimulus, scratches or licks itself and smells frequently. It runs rapidly to hide when a person approaches, or when an unexpected stimulus is presented. The work affectivity is employed to indicate the behavior of the cat to aproach the observer in order to be caressed.

The quantification of the behaviors evoked by d-amphetamine was easy because of the fixed positioned (immobility) the cats assumed after receiving the drug. This was true especially for the lateral head movements, immobility, olfaction and respiratory rate. For apomorphine, the quantification of the different behaviors was more difficult, due to the almost continuous displacement of the cat, especially with the higher doses. However, it was possible to quantify the duration of the olfaction, motility and anxiety. The increase in motility was measured according to the number of meters the cats walked or ran per unit time, and also the duration of such behavior. For anxiety, the presence of the symptoms described above allowed us to quantify the duration of this behavior.

For statistical analysis we employed either the Student's t-test or the one-way ANOVA test, according to the problem studied.

RESULTS

The control injection of a fixed volume of NaCl 0.9% did not evoke any change in behavior.

Amphetamine

The 0.1 mg/kg dose produced changes in motor activity. Hypomotility, characterized by the adoption of a fixed position, was observed. The mean duration of the fixed position was 40 min (Fig. 1). A significant increase of the respiratory frequency over the control value was recorded (Fig. 2). The relations of the cats with the observers, and the state of alertness, were not modified.

The administration of 0.5 mg/kg evoked some behavioral changes that were not substantially different from those elicited by the previous dose. The immobility period attained a mean duration of 48 min (Fig. 1). The state of alertness increased, and a loss of affectivity towards the observers appeared. The respiratory rate also increased significantly over the control values, but not much in relation to the 0.1 mg/kg dose (Fig. 2).

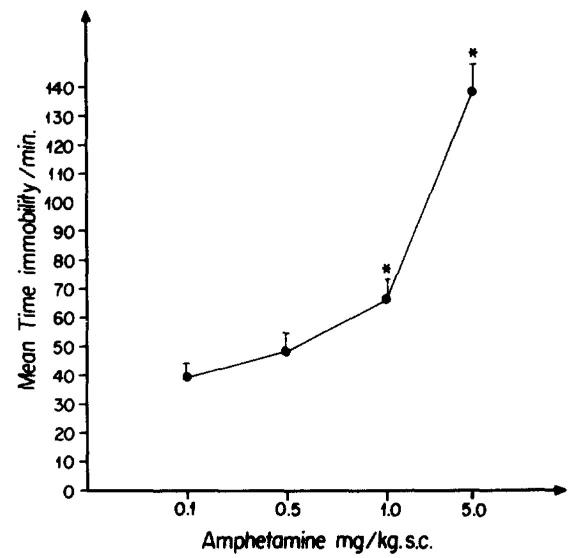

FIG. 1. Effect of d-amphetamine on motor behavior in adult cats. Dose-response curve of mean time immobility. The figure shows the effects of amphetamine on cat's mean immobility. Abscissa: doses of amphetamine mg/kg SC; ordinate: mean time immobility after drug administration. The differences of the means comparing the 5.0 mg/kg dose with the three minor doses are statistically significant (p<0.01). The difference between the 1.0 mg/kg dose with the 0.1 dose is also significant (p<0.05). Statistical method employed: one-way ANOVA test. Bars=standard error. *p<0.01.

Doses of 1.0 and 5.0 mg/kg elicited important behavioral modifications that were qualitatively similar for both doses, but with some quantitative differences. All the 17 cats showed an important decrease in mobility with both doses; with the 5.0 mg/kg dose, the period of fixed position reached a mean value near 140 min (Fig. 1). In the first five min after injection, the animals adopted a seated or sphinx position, or they laid down on the floor and remained there during all the observation period. One of the cats stood on its feet, without moving for a period close to 60 min. This important hypomotility was not due to a lack of motor capacity, since the animals walked rapidly, returning to the original place, when they were removed from such location.

Besides this hypomotility, the cats showed indifference to their environment and a clear loss of affectivity to the observers, not searching to be caressed. Slight fear was observed only in 3 cats, and only during the first 5 min after receiving amphetamine. With both 1.0 and 5.0 mg/kg doses, a behavior was observed that revealed an important modification of the cat's usual conduct. When the animals urinated, they remained in the same position over the floor that contained the urine. This contrasted with the usual behavior of the cat in relation to its excretes. An increase in respiratory rate was observed in all the animals, with a mean increase in frequency of 50% for the 1.0 mg/kg dose, and 180% for 5.0 mg/kg dose. All the animals showed stereotypy, consisting of slow horizontal bilateral head movements. The mean number of movements was 10.6 and 23.8 for 1.0 and 5.0 mg/kg doses respectively. This behavior appeared very irregularly with the 0.1 and 0.5 mg/kg doses, and this fact prevented the construction of a dose-response curve.

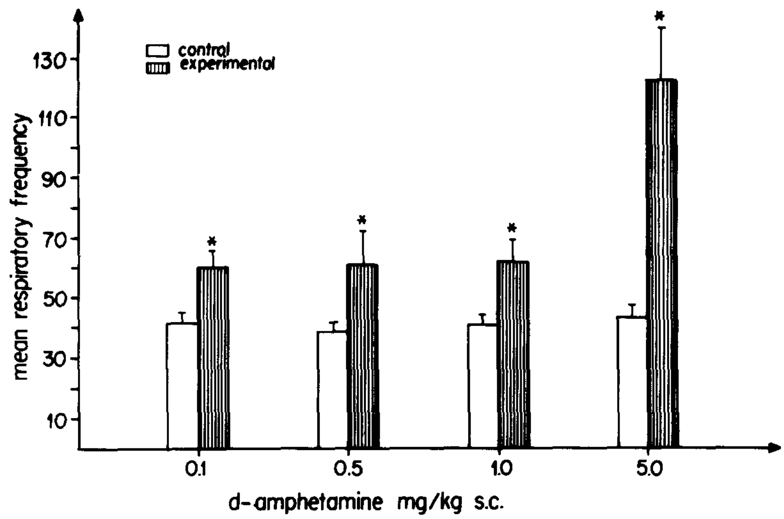

FIG. 2. Comparative analysis of mean respiratory frequency before and after four progressive doses of d-amphetamine in adult cats. The figure compares for each dose of d-amphetamine the mean of maximum respiratory frequency before and after drug administration. $p<0.05$ according to the dependent paired Student's t-test for each dose. Bars=standard error. *$p<0.05$.

Figure 3 shows the main behaviors induced by a 5 mg/kg SC dose of d-amphetamine. The latency and duration of each behavior was analyzed. Immobility showed the shortest latency and longest duration; lateral head movements showed the longest latency, and olfaction the shortest duration.

The following autonomic effects were observed: salivation and micturition in most animals, defecation in 4 animals. None of the cats with any dose of amphetamine showed aggressivity.

With any dose employed, the first behavioral changes appeared between 3–10 min after injection. The complete series of symptoms were present about 30 min after drug administration. The tendency to normalization with the two higher doses was a slow process and it started 60–90 min after drug injection.

Apomorphine

The 0.1 mg/kg dose did not induce important behavioral changes. In 10 cats a decrease in motor activity was observed. The rest of the cats continued their walking and exploring behavior as in the control period. No change in affectivity behavior of the animals in relation to the observers was seen. No modification of the respiratory rate was observed in any animal.

The administration of 0.5 mg/kg produced important behavioral modifications. Most of the cats showed hypermotility (Fig.

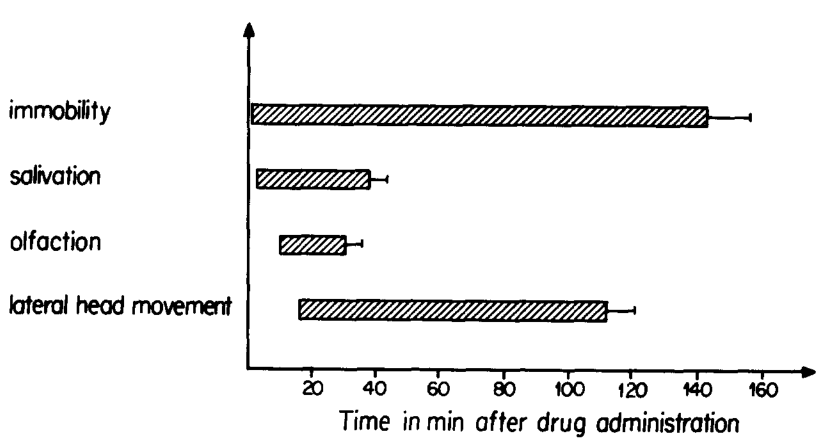

FIG. 3. Principal behaviors induced by d-amphetamine administration (5.0 mg/kg SC) in adult cats. Latency and duration of each behavior. Four of the main behaviors evoked by 5.0 mg/kg of d-amphetamine are shown according to their latencies and duration. Immobility shows the shortest latency and longest duration; lateral head movement, the longest latency and olfaction the shortest duration. Bars=standard error.

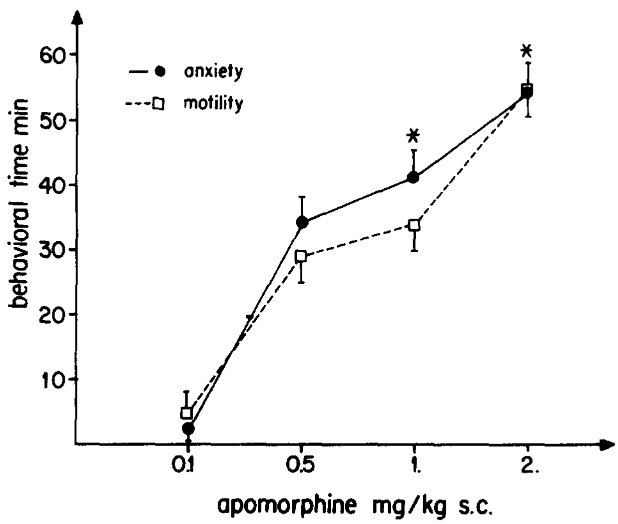

FIG. 4. Effect of apomorphine on cat's motor behavior and anxiety. Dose-response curve. The figure shows two curves, one for the increase in motility and a second curve for the induction of anxiety by progressive doses of apomorphine. $p<0.01$ comparing the differences of the mean values between the 2.0 mg/kg dose with the 0.1 and the 0.5 doses. $p<0.05$, when the comparison is done between the 2.0 with the 1.0 mg/kg doses. $p<0.05$, comparing the 0.1 with the 0.5 mg/kg doses. The p values are the same for both curves. Statistical procedure: one-way ANOVA test. Bars=standard error. $^*p<0.01$.

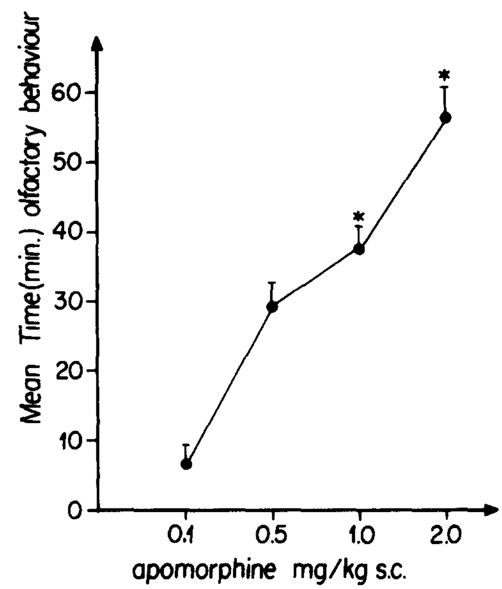

FIG. 5. Effect of apomorphine on olfactory behavior in adult cats. Dose-response curve. The figure shows a dose-response curve when the duration of the olfactory behavior is analyzed in relation to progressive amounts of apomorphine injected. $p<0.01$ comparing the effects produced by the 2.0 mg/kg dose with the 0.1, 0.5 and 1.0 mg/kg doses. $p<0.05$ when the difference between the 0.1 and 0.5 mg/kg doses is anlayzed. $p<0.05$ corresponds to the comparison between the 1.0 and 0.1 mg/kg doses. Statistical procedure: one-way ANOVA test. Bars=standard error. $^*p<0.01$.

4), which could adopt one of these three forms: 1) continuous walking between two points on a fixed path selected by the cat; 2) continuous walking in several directions; and 3) continuous movement of the cat that advanced a short path and then motioned backward, repeating this type of motor activity for long periods of time. These three types of hypermotility performed in a repetitive form, without any apparent purpose, constituted a modality of stereotypy. The motor behavior started approximately about 5 min after apomorphine administration and lasted 30–60 min. Frequently the cat moved its head, but these movements were rapid in all directions, and contrasted with the slow, rhythmic bilateral head movements of the cat treated with amphetamine.

Another motor behavior—which did not appear with amphetamine—was limb flicking, especially of the hind legs; it was observed in half of the cats with the 0.5 mg/kg dose of apomorphine.

An important change in behavior is the apparition of fear or anxiety (see the Method section) 2–3 min after the drug administration. The cat ran to hide itself under the table. It appeared in 70% of the animals with the 0.5 mg/kg dose, and the mean duration with this dose was approximately 30 min. Besides fear, the cats showed an increase in the state of alertness and hyperreactivity characterizing this last behavior by a rapid orientation of the head of the animal to auditory or visual stimuli. A decrease in the behavior of trying to aproach the persons which recorded their conduct was also observed. No aggressivity was seen.

Of the autonomic manifestations, one of the cats vomited, two cats defecated and four presented micturition. Changes in the respiratory rate were not observed in the animals that did not present hypermotility. In those which walked continuously, the respiratory frequency could not be recorded.

The 1.0 and 2.0 mg/kg doses produced a marked intensification of the behavioral changes seen with the 0.5 mg/kg dose. Approximately 5 min after apomorphine administration, the cats ran to hide themselves, showing in this form an anxiety or fear behavior (Fig. 4). They presented hyperreactivity in relation to any stimulus, especially auditory. They started to walk rapidly or to run, always following a path selected by each animal, and maintained these motor behaviors for approximately 50 min. The increase in motor activity was dose-dependent (Fig. 4). Limb flicking, especially of the hind legs, was observed in all cats, and it is a second modality of stereotypy.

While moving, all the cats presented another behavior: an increase in olfactory activity that accompanied the walking activity. This olfaction behavior is the third modality of stereotypy observed in cats treated with apomorphine (Fig. 5).

In three cats, a behavior suggesting the presence of hallucinations appeared with the 2.0 mg/kg dose. The cats stopped in their continuous walking and stared at any object; then they threw a whack to an imaginary enemy and rapidly jumped back. Another behavior appeared with the two highest doses, especially with the 2.0 mg/kg dose: when the animal developed a large increase in motility, it did not care about its surroundings, and fear, affectivity and hyperreactivity disappeared.

Behaviors like licking and scratching appeared as an important activity in 6 animals with the highest doses. Autonomic effects, like salivation, were seen in all cats; micturition in six and defecation in two. Piloerection was obseved in three animals. It was a symptom difficult to record, due to the persistent and rapid walking of most cats treated with high doses of apomorphine.

The behavioral changes (especially olfaction) apeared 2–3 min after drug administration and the effect reached a peak about 15–20 min. With the 0.5 mg/kg dose, the signs of normalization began to appear about 30 min after apomorphine injection. With

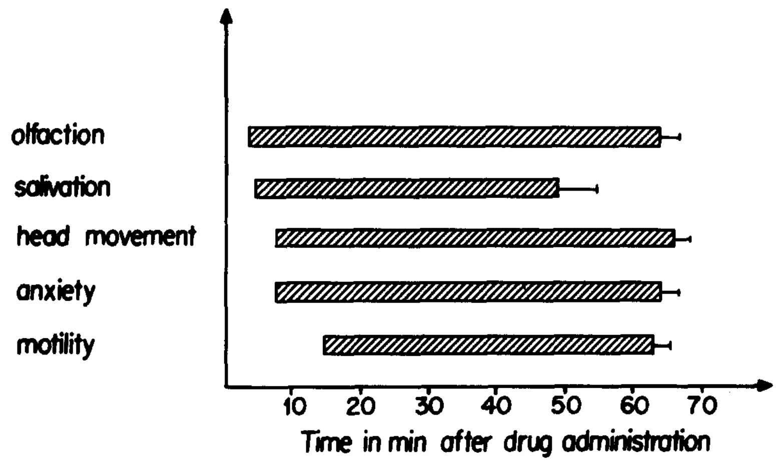

FIG. 6. Principal behaviors evoked by apomorphine administration (2.0 mg/kg SC) in adult cats. Latency and duration of each behavior. Five behaviors evoked by the 2.0 mg/kg dose of apomorphine are shown. The shortest latency corresponds to olfaction which also shows the longest duration. The longest latency is for the increase in motility. Bars=standard error.

1.0 to 2.0 mg/kg, normalization started to appear, aproximately between 60–90 min after drug administration, especially the last figure when the dose given was 2.0 mg/kg. Normalization was more rapidly attained with apomorphine than with amphetamine. With 1.0 mg/kg of apomorphine complete recovery was observed near 90 min after drug administration, and with the 2.0 mg/kg, recovery was attained about 120 min after apomorphine injection.

In Fig. 6 the latencies and durations of the principal behaviors induced by apomorphine (2 mg/kg SC) are analyzed. Olfaction and salivation appear with the lowest latencies (<5 min). Next latencies are those of anxiety and head movements (7 min) and finally hypermotility (15 min). The longest durations are observed in relation to olfaction, head movements and anxiety.

DISCUSSION

Our experiments demonstrated that amphetamine and apomorphine evoked in cats different behavioral reactions. Most of these reactions showed a significant dose-response relationship. As regards amphetamine, we found that it did not induce hypermotility. This is in contradiction to what has been reported in other animal species like the rat. With higher doses (1.0 and 5.0 mg/kg), the animals became hypoactive, either sitting or lying on a fixed place, for rather long periods of time (60 min or more). The only stereotypy observed was a bilateral and rhythmic slow movement of the head. The animal appeared indifferent to the environment and unconcerned about the observers. Finally, a dose-dependent increase in respiratory rate was observed.

Regarding the responses to the administration of apomorphine, we recorded a dose-dependent increase in motor and olfactory activities, as well as limb flickings, thus displaying three different types of stereotypes. The animals had the appearance of being frightened; they showed hyperreactivity to sudden stimuli, and with the higher doses they showed complex movements, as if they had hallucinations. When the motor activity markedly increased, a kind of indifference to the whole environment appeared.

The role played by several structures and neurotransmitters of the CNS on the reactions induced by amphetamine and/or apomorphine is still under investigation. Various reports indicate that the motor effects induced by these drugs would result in the rat from an action on the dopaminergic limbic system, like the nucleus accumbens and tuberculum olfactorium (7, 8, 18). On the other hand, the stereotypes appeared to be produced by an action on the neostriatum (9,18). These data, however, have not been confirmed by other researchers (4–6, 15, 22).

Although the mechanisms of the behavioral differences elicited by amphetamine and apomorphine have not been clarified, it has been postulated that these drugs may activate different dopaminergic systems (3). It has also been hypothesized that they could interact with other neurotransmitters. It has been shown, for instance, that both the cholinergic (19, 23, 32) and the serotoninergic systems (1, 2, 27, 34) can interact with amphetamine and apomorhpine, and also that amphetamine is a releaser not only of DA (28), but also of noradrenaline (26). With regard to apomorphine, there are experimental evidences that in low doses it acts on presynaptic receptors (13,16) and at higher concentrations it activates the postsynaptic receptors (13,16), though without releasing noradrenaline. It could be suggested, therefore, that the release of DA and noradrenaline by amphetamine, and only the activation of DA receptors by apomorphine, are involved in the different behavioral responses induced by these two drugs. However, this hypothesis is not substantiated by the results of experiments in rats which were almost depleted of their brain noradrenaline content and showed no alteration in locomotor activity when amphetamine was administered (10).

Although it has been postulated that the released noradrenaline by amphetamine could be responsible, in the rat, for the increased motor activity (10, 11, 31), our experiments in cats with amphetamine, with any doses used, produced instead of hypermotility a state of hypomotility. Thus, we think that it would be rather difficult to explain the behavioral responses obtained in the cat as a result of the release of both DA and noradrenaline by amphetamine.

Nickolson (26) hypothesized that the different effects of apomorphine would implicate the existence of a number of receptor populations with particular pharmacological properties. The variance between the effects of apomorphine and amphetamine could be explained, according to Nickolson (26), by the abovementioned populations of DA receptors.

The increase in respiratory rate observed in our experiments with amphetamine appeared in animals in a state of hypomotility. Mediavilla *et al.* (24) attributed this increase to a stimulatory action of amphetamine on the respiratory center. According to these authors, this effect is mediated through a central alpha-adrenergic mechanism.

As previously stated, in most behavioral reactions induced by amphetamine or apomorphine, a significant dose-response relationship was found. In the case of amphetamine, sensitization could be raised to explain the results obtained with this drug (14,30), owing to the fact that we administered progressive doses of amphetamine (see the Method section). However, we obtained similar dose-response reactions whether amphetamine was administered in increasing or decreasing dose series. Furthermore, sensitization to apomorphine has not been shown; on the contrary, this drug produces tolerance that lasts approximately 24 hr (33).

Levine *et al.* (20) presented data obtained in cats that received three doses of amphetamine (1, 2 and 4 mg/kg IP). The 1.0 mg/kg dose was near threshold to evoke behavioral responses. The medium dose produced increases in locomotion and head movements, while the highest dose induced marked increases in the frequency of head movements and reduced locomotion. The results obtained by Levine *et al.* (20) coincided only in part with the data obtained in our experiments, since we recorded hypomotility with all doses employed. As we worked with mongrel cats (street cats) our results cannot be criticized as an effect obtained in only one strain of these animals.

Apomorphine has also been given to cats. Trulson and Crisp (33) administered doses from 2 to 10 mg/kg and found that the drug evoked little or no behavioral responses when 2.0 mg/kg was injected; 4.0 mg/kg induced the greatest hypermotility and other behavioral reactions while 6, 8 and 10 mg/kg resulted in prominent stereotypes. Thus, Trulson and Crisp (33) reported that apomorphine did not produce dose-response reactions. We think that the stereotypy that resulted from the large doses of apomorphine that they employed masked other behavioral responses.

The sex factor did not play, apparently, any role in our experiments.

In summary, our experimental series shows that apomorphine and amphetamine elicit marked differences in behavioral responses in adult cats. These differences appeared in relation to motor activity, stereotypes and also in responses that could be related to the mental sphere. In relation to amphetamine, we found with all doses employed the induction of hypomotility, contrasting with the usual hypermotility described in other animal species like rats and mice. The mechanisms of these different behavioral responses have not been clarified.

ACKNOWLEDGEMENTS

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