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Study of the Behavioral Effects of Bilateral Nucleus Accumbens Lesions on Amphetamine and Apomorphine in Adult Cats

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MOTLES E., C. INFANTE, G. SANCHEZ AND M. GONZALEZ. *Study of the behavioral effects of three types of bilateral nucleus accumbens lesions on amphetamine and apomorphine in adult cats.* PHARMACOL BIOCHEM BEHAV **59**(3) 619–626, 1998.—The aim of the present work was to study the effects of three different types of bilateral lesions performed on the nucleus accumbens, upon the behaviors elicited in adult cats by parenteral administration of amphetamine and apomorphine, and to obtain an understanding of the functional role played by the cited structure. To this end, 10 cats received bilateral injections of 6-OHDA, 18 μg in each accumbens; 8 cats received a similar treatment with ibotenic acid (20 μg), and 11 cats were submitted to bilateral electrolytic damage. Before and after performing these lesions, in separate sessions, amphetamine (2.5 mg/kg SC) and apomorphine (2.0 mg/kg SC) were administered and their respective behaviors were compared. Besides, in a group of 10 cats, 6 of them were bilaterally injected with the above cited dose of 6-OHDA into the accumbens to determine dopamine concentration and the other four served as control. In three cats, ibotenic acid (20 μg) was unilaterally injected into the accumbens for histological analysis. The contralateral structure served as control. Finally, four cats were sham operated. The results obtained show that the accumbens in cats participates in locomotion, in stereotyped motor behaviors, and in emotional fear-like behavior. Its role in the production of motor behaviors apparently is not as important as has been reported in rodents. © 1998 Elsevier Science Inc.

Cats Behavior Nucleus accumbens Amphetamine Apomorphine 6-Hydroxydopamine Ibotenic acid Electrolytic lesion

THE parenteral administration of a dopaminergic agonist, like amphetamine and apomorphine, evoke different types of behaviors. Those produced by amphetamine are mostly explained by an increase in dopamine (DA) release and a decrease in the reuptake of this drug. Amphetamine also induces an increase in the release of serotonin, acethylcholine, and noradrenaline. On the other hand, apomorphine activates the dopaminergic system by its binding to dopaminergic receptors (13,15,24).

Most studies on the behavioral effects of amphetamine and apomorphine reported in the literature have been carried on in rodents. Very few studies have been performed in cats. It is interesting to point out that the cited dopaminergic agonist drugs do not evoke in cats the same behaviors as those observed in rodents. For instance, amphetamine in rodents induce increase in locomotion, while in cats it evokes lack of locomotion (16), which lasts from 3 to 6 h. Besides, these drugs elicit in cats more varied behaviors than those observed in rodents (16).

In previous works we have studied in the cat the role played by different neurotransmitter systems, such as the serotoninergic, cholinergic, noradrenergic, and opioid (17–19, 22), on the behaviors evoked by amphetamine and apomorphine in adult cats, and the role of the dopaminergic D_1 and D_2 receptors (20,21). Recently we started to study in the adult cat the role played by several cerebral structures, which receive a rich dopaminergic innervation, as mechanisms of production of the behaviors accompanying the administration of amphetamine and apomorphine. In the present work we selected the nucleus accumbens (Acc), which receives a rich dopaminergic innerva-

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tion from the neurons of the ventral tegmental area, and that has been intensively studied in rodents (1–5,11,12).

The reasons to select the Acc is twofold: 1) its richness in dopaminergic innervation and; 2) numerous reports in the literature (1,3,9–12,14,25) have emphasized its important role in the production of locomotor activity; however, these results have been controverted by other reports (2,6,27).

The aim of the present work is to study the role of the Acc in the production of the behaviors elicited by dopaminergic agonists (amphetamine and amphetamine) in adult cats, and to this end behaviors evoked by amphetamine and apomorphine before and after lesioning the Acc were compared. In three different experimental designs, the Acc were damaged with 6-OHDA in one of them, and in the two other procedures, the lesions were performed with ibotenic acid or electrolysis.

METHOD

Animals

Forty-six adult mongrel cats of both sexes were employed, and distributed in the following way: 1) 10 cats received bilateral intraaccumbens injection of 6-OHDA; 2) 8 cats were bilateral injected into the Acc with ibotenic acid; 3) 11 animals were lesioned bilaterally through electrodes implanted in the Acc; 4) in 6 cats both Acc were injected with 6-OHDA, with the same doses that were employed in the first group of cats, and they were assigned only to DA concentration analysis; 5) in another group of 4 cats, no 6-OHDA was injected in the Acc, and they were appointed to DA concentration determination as a control group; 6) in a group of 3 cats, a unilateral ibotenic acid lesion was performed to study the histological changes produced by the cited drug. The contralateral Acc served as control. The amount of ibotenic acid unilaterally injected was similar to the amount injected in each Acc in the second group of cats; 7) finally, in 4 cats, sham operated, the solvents employed with 6-OHDA (2 cats) and the solvent employed with ibotenic acid (2 cats), were injected into the Acc and amphetamine and apomorphine were administered before and after the solvent administration.

General Procedure

All cats received in separate sessions parenteral administration of amphetamine (2.5 mg/kg SC) and apomorphine (2.0 mg/kg SC). These doses were selected according to the results obtained in a previous dose–response study (16). The behaviors were observed by three experimenters, who tried to interfere as least as possible with the animals. Only one of the researchers knew the drug administered. The behaviors were recorded in a room 5 × 6 m, well lighted and sound proof, to which the cats were previously accustomed. In the room there were three chairs, a shelf, and a writing desk. The spontaneous behavior of the animals were recorded during a 30-min period, previous to the drug administration. The behaviors were recorded in a protocol ad hoc, and the observation lasted until the cats reached the control condition. When apomorphine was injected the duration of the examen was usually about 90 min. With amphetamine the control condition was reached after 3–6 h. After obtaining the behavioral data from amphetamine and apomorphine administration, the cats were subjected to surgery. Under nembutal anesthesia (30 mg/kg IP), and aseptic conditions, the cats were stereotaxically and bilaterally injected with 6-OHDA in one experimental design, and in another one the same procedure was done with ibotenic acid. In a third group, electrodes were implanted in both Acc to perform electrolytic lesions. After complete recovery from surgery, about 14 days, the cats again received the same doses of amphetamine, and the behaviors recorded were compared with those induced previous to the lesions.

Surgical Procedures

Bilateral administration of 6-OHDA into the Acc. The coordinates selected, according to the Jasper and Ajmone-Marsan Atlas (8) were: A: 17.0, L: 2.0, V: −1.0; A: 16.0, L: 2.5, V: 0, and A: 15.0, L: 3.0, V: 1.0. The amount injected in each coordinate was 1.5 μl, and the total drug amount injected in each Acc was 18 μg. The drug was freshly prepared in NaCl 0.9%, and 0.2 mg/ml of ascorbic acid was added to avoid oxydation. The concentration of the drug was 4 μg/μl. All cats were injected 1 h before surgery with 20 μg/kg SC of desmethylimipramine, to avoid damaging the noradrenaline neurons.

Bilateral injection of ibotenic acid into the Acc. This drug was injected at the following coordinates: A: 17.0, L: 2.0, V: −10; A: 16.0, L: 2.5, V: 0. The drug was dissolved in NaCl 0.9%, additioned with buffer phosphate. The amount injected in each coordinate was 1.0 μl. The total drug amount injected in each nucleus was 20 μg.

Bilateral electrolytic lesion of the Acc. Two twisted bipolar stainless steel electrodes, with intertip distance of 1 mm, isolated excep at the tip, were implanted in the Acc according to the coordinates: A: 16.5, L: 2.0, V: 0; and A: 16.0, L: 2.5, V: 0. Electrolytic lesions were performed through 3 mA DC current for 10 s.

Behavioral Protocol

The following variables were recorded.

Alertness: 0 = the cat is not alert. It does not respond to enviromental stimuli like finger snapping, movements of the experimenter, or any noise that could be hear in the laboratory. The cat sits quietly on the floor, its eyes closed or open. The pupils not dilated. 1 = normal orienting responses to finger snapping. 2 = increasing speed of orienting response to finger snapping.

Indifference (social interaction): 0 = the cat spontaneously approaches the observer. 1 = the cat has to be repeatedly called before approaching the observer. 2 = the cat ignores the observers or the objects present in the room.

Fear-like behavior: 0 = the cat allows the close approach of the experimenter. 1 = the cat withdraws if the experimenter tries to approach it, or it adopts a crouching position and moves its head forcefully and frequently; eyes wide open; pupils dilated. 2 = the cat spontaneously withdraws from the experimenter, looking actively for a hinding place, where it could stay for different periods of time. 3 = the cat flees when the experimenter approach it; it shows increased locomotor activity, and searches location where it could hide, running from one place to another.

Locomotion: 0 = the cat is motionless. 1 = the cat walks normally (control conditions). 2 = the cat walks continually. 3 = the cat runs and jumps.

Head movements: 0 = no head movement. 1 = less than 10 head movements per min. 2 = 10–20 head movements per min. 3 = more than 20 head movements per min.

Head shakings: 0 = no head shaking. 1 = less than 10 head shakings per min. 2 = 10–20 head shakings per min. 3 = more than 20 head shakings per min.

Limb shakings: 0 = no limb shaking. 1 = less than 10 limb shakings per min. 2 = 10–20 limb shakings per min. 3 = more than 20 limb shakings per min.

The meaning of some of the behaviors is self-explanatory, except for alertness, indifference (social interaction), fear-like behavior, and head shaking. In relation to alertness, score 0 indicates lack of it; the cat does not respond to any stimuli, and the animal can have its eyes open or closed. Normal alerness means that the cat responds to the enviromental stimuli (noise) or those originated by the experimenter, like finger snapping. The response consists in orienting its head towards the stimuli, opening its eyes, and sometimes trying to approach the experimenter; increase in alertness is indicated by a rapid orienting response of the cat to any stimuli produced in the laboratory.

By indifference (social interaction) we mean the ability of the cat to interact with the observers. All the cats, when brought to the laboratory to which they have been previously accustomed, approach the observer trying to be caressed. It is a very close contact. After the drug administration the cat does not approach the experimenter, and it is possible to establish several stages in this behavior; finally, in its most intense manifestation, the cats behaves by completely ignoring the presence of the observer. The different scores we have established show a progressive intensification of the cited behavior. In relation to fear-like behavior, it is a very clear response, especially when apomorphine is administered. As cited previously, when the cat is brought to the laboratory its attitude is very friendly towards the observer, trying to be caressed. After the drug administration the animal adopts a crouching position, moving its head rapidly towards the experimenter or to any noise that is heard in the laboratory, its eyes wide open, and the pupils dilated. In a later stage the cat shows a retreat response, looking for a place where it could hide. Head shaking consists in an abrupt and short shaking of the cat's head lasting from 3–5 s.

The agreement of the data recorder by the three observers was about 90%.

Biochemical Analysis

In six cats, 6-OHDA was bilaterally injected into the Acc, employing the same doses administered to the 10 cats whose behaviors were recorded. In another four cats, the Acc was taken out for DA concentration analysis and for comparison with DA concentration of the group injected with 6-OHDA.

In the first group, 14 days after 6-OHDA injection, and under deep nembutal anesthesia (40 mg/kg IP), the brain was rapidly removed, frozen with CO_2, and 4.6 mg of the Acc were taken out with the help of a magnifier. The Jasper and Ajmone-Marsan Atlas (8) was employed. The sample was received in 0.05 ml of 0.2 N perchloric acid containing 0.5 mM sodium metabisulfite. This solution was maintained cooled on ice. The samples were homogeneized and centrifuged at $10{,}000 \times$ g. The supernatant was stored at $-70°C$. Concentrations of DA were determined by HPLC with electrochemical detector, using a glassy carbon electrode. DA and DHBA (the internal standard) was chromatographed on a CR-C18 column. The isocratic mobil phase was: 0.7 mM sodium octil sulfate, 1.0 mM EDTA, 8% metanol, and 3 mM citric acid. The DA concentration was determined by the internal standard method, measuring the peak of DA and DHBA, and the quotient DA/DHBA interpoled in a calibration curve done in the same way. Concentration of DA is expressed as nanogram per mg of wet weight tissue.

Histological Procedure

Three cats received a unilateral injection of 20 μg of ibotenic acid, following the same surgical procedure as described for the eight cats that received bilateral injections of this drug. The contralateral Acc served as control. After 14 days the cats were anesthetized with sublethal doses of Nembutal IP, and the brain was transfused transcardiacally with 500 ml of Na Cl 0.9%, followed by 500 ml of 4% paraformaldehyde. Then the brain was removed and maintained for 2 days in a freshly prepared fixation solution. Afterwards, the brain was sliced with the help of a freezing microtome; the section thickness of 50 μm, was obtained at 100-μm intervals, mounted on slides, and stained with 1% toluidine blue.

Drugs

Racemic amphetamine was obteined as a gift from Laboratorio Chile (Santiago, Chile). Apomorphine was purchased from the same Laboratory. Desmethylimipramine, ibotenic acid, and 6-OHDA were bought from RBI.

Statistical Procedure

The nonparametric Wilcoxon signed rank test was employed. The level of statistical significance was $p \leqslant 0.05$.

In the tables we compare the duration in min of the behaviors produced by amphetamine, administered before and after the lesion performed in the nucleus accumbens. The same thing for apomorphine. No control condition is indicated in the tables, because in such situation the cat does not show the behaviors evoked by amphetamine or apomorphine, and consequently, we cannot quantify in minutes behaviors that are produced by the dopaminergic agonist drugs and that are not present in the control condition.

In the control state that does not appear in the tables, the behavioral characteristics of the cat according to the above cited protocol are: alert 1, locomotion 1, fear 0, indifference 0, head shaking 0, head movement 0, and limb shaking 0 (see the Method section). The numbers between brackets that appear in the tables indicate the intensity of the behaviors that were considered in the statistical analysis. The intensities that are not shown in the tables did not show statistical differences, or as happens with score 3, the numbers of animals were small. In relation to locomotion and amphetamine administration it was considered score 0 (inmobility) because this is the main effect of amphetamine, while in relation to apomorphine, which produces an increase in locomotion score 2, was analyzed statistically.

RESULTS

Dopamine Concentration Assay in the Acc

Six cats received a bilateral injection of 18 μg of 6-OHDA in the Acc following the same procedure described for the cats in whom a behavioral study was performed. Another four cats, which were not injected with this drug, served as control. The amount of Acc removed in the 6-OHDA cats was 4.6 ± 1.74 mg, and in the control animals 4.5 ± 1.29 mg. The mean and standard deviation of DA concentration in the treated cats was 1.35 ± 0.16 ng/mg and in the control cats 4.77 ± 2.68 ng/mg. The reduction in DA concentration was 71.7%, and the difference was statistical significant ($p < 0.05$).

Histological Finding of Ibotenic Acid Lesion of the Acc

The results are analyzed in Fig. 1. Part A of the figure belongs to the intact Acc. The neurons are of a small size, round, with a central nucleus. The glial cells are distributed uniformly through the preparation. Part B shows the lesioned

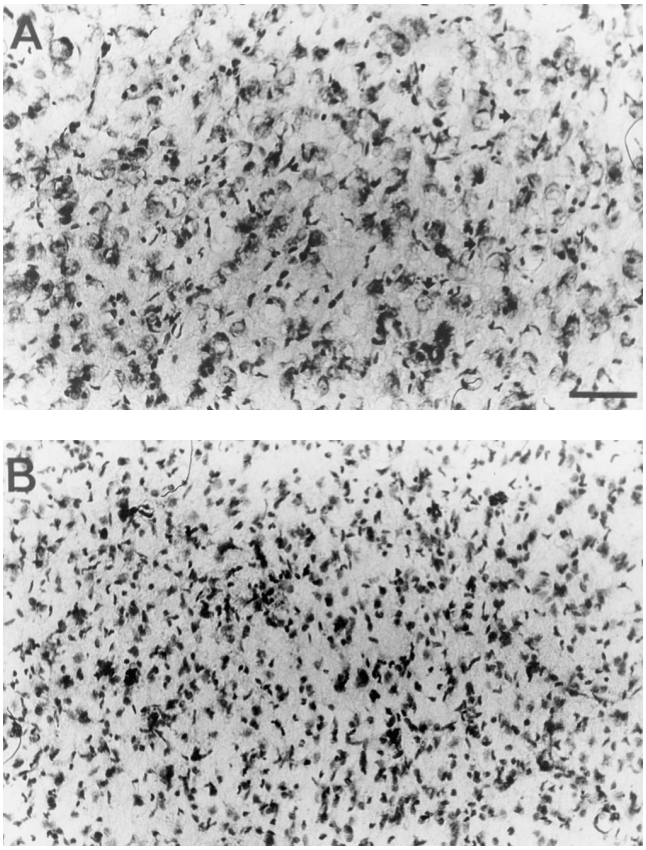

FIG. 1. (A) Belongs to the nonlesioned accumbens. The neurons are of small size, rounded, with a central nucleus. The glial cells are distributed uniformly through the preparation. (B) Correspond to the lesioned nucleus with ibotenic acid. The neurons have disappeared and have been replaced by glial cells. Both photographs represent equivalent anatomical areas. Magnification 200×. Bar calibration in photograph A = 100 μm, is also valid for photograph B.

Acc. The neurons have disappeared and only glial cells are observed.

Electrolytic Lesion of the Acc

The photograph shown in Fig. 2 corresponds to a coronal section at the stereotaxic plane A = 16.0, according to Jasper and Ajmone-Marsan Atlas (8). A bilateral destruction of the Acc can be observed. White arrows show the extension of the electrolytic lesion produced by a DC electric current of 3 mA for 10 s.

Behavioral Results

Behavioral effects of bilateral 6-OHDA of the Acc. The results are described in Table 1. In the "Behavior Column" the numbers between parentheses indicate the intensity of the behavior that is analyzed (see the Method section). The selected intensities were the most representative of the indicated behavior, and most cats belonged to this intensity. The numbers in the other columns (except the p column), indicate the median of each behavior expressed in min.

After 6-OHDA damage it can be observed that the injection of amphetamine produced less immobility compared with the prelesion administration (as cited, amphetamine in cats produces immobility). The table shows that before 6-OHDA lesion, administration of amphetamine produced immobility (median 150 min), and after the neurotoxic local injection, the immobility was reduced to a median of 100 min. This difference indicates that the cat could walk normally during 50 min. When the cat is treated with amphetamine, the usual behavior is immobility. When this disappears, it walks normally, and its locomotion never increased over normal. This difference in the immobility period was statistically significant ($p < 0.04$).

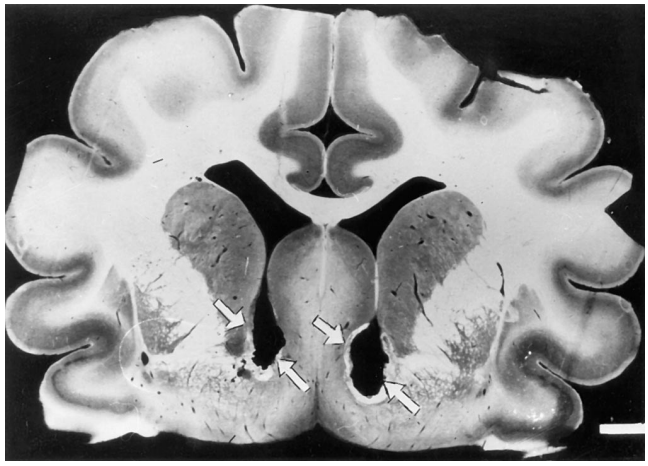

FIG. 2. Photograph corresponding to a coronal section of a cat's brain at stereotaxic plane A = 16 (atlas of Jasper and Ajmore-Marsan). An extensive bilateral electrolytic lesion of the accumbens nuclei are indicated by white arrows. Bar calibration = 2 mm.

Apomorphine after 6-OHDA, only provoked a decrease in fear-like behavior.

Behavioral effects after ibotenic acid lesion of the Acc. Table 2 analyses the effects of ibotenic acid, and it follows the same scheme as described in Table 1. In relation to amphetamine, it can be observed a significant decrease in fear-like behavior. No changes in the other behaviors were recorded. On the other hand, apomorphine, after the damage, evoked a significant decrease in fear-like behavior, and a reduction in the increase in locomotion that this dopaminergic agonist produces usually in cats.

Behavioral effects after electrolytic lesion of the Acc. Table 3 shows the effects of electrolytic lesion upon the behaviors elicited by amphetamine and apomorphine after electrolytic damage of the Acc. No changes in the behaviors evoked by amphetamine were observed. However, when apomorphine was administered, a significant increase of three types of stereotypies (head movements, head shaking, and limb shaking) were recorded.

DISCUSSION

The behavioral role played by the Acc has been extensively analyzed in rodents, specially in rats, and the majority of the reported works shows that when this structure is challenged by dopaminergic agonists, activation of motor activity ensues (1,3–5). However, these results have been controverted by other researchers (2,6,27).

Our interest to study the behavioral role of the Acc in the cats was based on several considerations: (a) the scarcity of reports about Acc function in cats; (b) the controverted results reported about Acc function in rats and; (c) the differ-

TABLE 1

COMPARATIVE ANALYSIS OF THE EFFECTS OF BILATERAL 6-OHDA LESIONS OF THE NUCLEUS ACCUMBENS UPON THE BEHAVIORS EVOKED BY AMPHETAMINE AND APOMORPHINE IN ADULT CATS

	Amphetamine (n = 10) Median duration (min)			Apomorphine (n = 10) Median duration (min)		
Behaviors	B	A	p-Value	B	A	p-Value
Alertness	125	95	NS	85	60	NS
Range	0–200	0–480		20–120	30–150	
Fear-like behavior	0	0	NS	48	25	0.004*
Range	0–60	0–40		25–120	5–40	
Indifference (2) (social interaction)	138	125	NS	70	45	NS
Range	0–260	80–180		15–120	15–110	
Locomotion (0)	150	100	0.04*	(2) 58	50	NS
Range	0–260	0–200		0–60	0–75	
Head movements	156	143	NS	128	159	NS
Range	0–301	52–362		0–516	0–273	
Head shaking	—	—	—	20	34	NS
Range	—	—	—	5–390	0–85	
Limb shaking	—	—	—	3	12	NS
Range	—	—	—	0–42	0–144	

Statistical procedure: The nonparametric Wilcoxon signed-rank test. Level of significance: $p \leq 0.05$.

Number in parentheses represent the analyzed behavior's intensities. B and A: values of the median in min before and after Acc lesions with 6-OHDA.

NS = not significant.

* = indicate statistical significance

ences in behavioral responses found between rats and cats when amphetamine is parenterally administered. As cited in the introduction, amphetamine in rats elicits increase in locomotion, while in cats, the same drug evoked long lasting immobility (16). According to previous works, locomotor activity in rats appears importantly related to the Acc. (1,10,12).

In the present study we considered it necessary to design models in which different types of lesions were performed: (a) damage of the Acc with 6-OHDA a selective neurotoxic drug of dopaminergic fibers; (b) damage with ibotenic acid, which destroys the cells of the Acc, sparing the fibers and; (c) electrolytic lesion that destroys all cells and fibers. As the three procedures produce different types of damage, obviously no similar kind of behavioral modifications should be expected. In fact, when amphetamine was administered, the 6-OHDA damage provoked only a decrease in the duration of the immobility, which amphetamine elicits usually in cats; this result can be considered as an improvement in locomotion. In effect, in relation to amphetamine administration, the cat shows either a lack of locomotion or it walks normally. Amphetamine in this animal species does not evoke increased locomotion. In relation to apomorphine, the only effect observed was a decrease in fear-like behavior. When the damage was produced by ibotenic acid administration, a decrease in fear-like behavior was recorded both with amphetamine and apomorphine, and with this last drug, also a reduction in increased locomotion (which is usually observed when this drug is injected in cats) was observed. Finally, after electrolytic damage, no changes in amphetamine-evoked behaviors were observed, while with apomorphine a significant increase in three types of stereotypies were recorded. From an analysis of these results, the Acc in cats appears involved in locomotion and in stereotyped behaviors, while, in relation to fear-like behavior it seems that the Acc is also involved in emotional behavior.

Trying to explain some discrepancies reported in rats about the relation of the Acc with motor activities (2,6,27), Kelly and Roberts (12), and Kubos et al. (14) postulated that the Acc normally exerts an inhibitory effect upon mesencephalic motor regions. According to this hypothesis, when DA or another dopaminergic agonist drug is injected into the Acc, these drugs elicit an inhibitory effect upon Acc neurons, and therefore, the final result is an activation of locomotor function. Now, the improvement in locomotion observed in the present work, when amphetamine was injected, and the Acc damaged by 6-OHDA, cannot be explained by the cited hypothesis, because according to it, an increase in immobility should have been observed, and not an improvement of locomotion. In effect, 6-OHDA produces a drastic reduction in DA concentration, and according to the inhibitory hypothesis, locomotor inhibition must ensue; an opposite effect was recorded. It is worthwhile to point out that 6-OHDA lesion of the Acc not only damages the dopaminergic fibers ending in this structure, but also passing fibers, which reach finally the prefrontal cortex. In relation to this result, we have shown (7) that ablation of the prefrontal cortex that receives a rich dopaminergic innervation also significantly decreases the duration of the immobility behavior produced by amphetamine in cats. Then, it is possible that, in the effects observed with 6-OHDA damage of the Acc, and amphetamine administration, the prefrontal cortex could also be involved.

When the Acc is damaged by 6-OHDA, and the dopaminergic fibers innervating this structure are destroyed, denervation of the dopaminergic receptors is produced, and supersensitivity of such receptors must ensue (11). An increase in

TABLE 2

COMPARATIVE ANALYSIS OF THE EFFECTS OF BILATERAL IBOTENIC ACID LESIONS OF THE NUCLEUS ACCUMBENS UPON THE BEHAVIORS EVOKED BY AMPHETAMINE AND APOMORPHINE IN ADULT CATS

	Amphetamine (n = 8) Median duration (min)			Apomorphine (n = 8) Median duration (min)		
Behaviors	B	A	p-Value	B	A	p-Value
Alertness	75	30	NS	80	75	NS
Range	0–160	0–105		50–110	60–90	
Fear-like behavior	37	0	0.01*	70	12	0.003*
Range	0–90	0–40		0–120	0–65	
Indifference (2) (social interaction)	150	185	NS	90	45	NS
Range	20–260	0–275		45–120	0–80	
Locomotion (0)	150	147	NS	(2) 85	63	0.01*
Range	50–280	0–260		10–100	15–50	
Head movements	109	118	NS	68	48	NS
Range	0–193	0–309		0–443	0–182	
Head shaking	—	—	—	24	22	NS
Range	—	—	—	0–366	1–69	
Limb shaking	—	—	—	4	1	NS
Range	—	—	—	0–286	0–52	

For explanations of the different numbers and abbreviations see Table 1. Statistical procedure: The nonparametric Wilcoxon signed-rank test.

NS = not significant.

* = indicate statistical significance

TABLE 3

COMPARATIVE ANALYSIS OF THE EFFECTS OF BILATERAL ELECTROLYTIC LESIONS OF THE NUCLEUS ACCUMBENS UPON THE BEHAVIORS EVOKED BY AMPHETAMINE AND APOMORPHINE IN ADULT CATS

	Amphetamine (n = 11) Median duration (min)			Apomorphine (n = 11) Median duration (min)		
Behaviors	B	A	p-Value	B	A	p-Value
Alertness	112	82	NS	60	70	NS
Range	0–195	0–220		20–80	0–90	
Fear-like behavior	0	0	NS	15	18	NS
Range	0–110	0–0		0–80	0–65	
Indifference (2) (social interaction)	105	90	NS	63	65	NS
Range	20–220	0–210		20–100	5–105	
Locomotion (0)	100	67	NS	(2) 70	63	NS
Range	0–220	5–260		0–95	25–110	
Head movements	56	152	NS	0	35	0.01*
Range	0–172	0–226		0–140	0–226	
Head shaking	—	—	—	21	54	0.002*
Range	—	—	—	0-43	18–188	
Limb shaking	—	—	—	4	9	0.03*
Range	—	—	—	0–18	0–16	

For explanations of the different numbers and abbreviations see Table 1. Statistical procedure: The nonparametric Wilcoxon signed-rank test.

NS = not significant.

* = indicate statistical significance.

the behavioral effects of apomorphine administration should be observed (locomotion) but no such increase was recorded.

The damage with ibotenic acid, which destroys the cells but not the fibers, did not modify the amphetamine evoked immobility. It did elicit a reduction in apomorphine evoked increase in locomotion. As the ibotenic acid destroys the cells, the dopaminergic receptors located in these cells are also damaged, and consequently, they are not available for binding with the DA released by the spared dopaminergic fibers. Again, according to the inhibitory motor hypothesis role of the Acc, we should expect an increase in locomotion elicited normally by apomorphine, but the opposite effect was observed. A tentative explanation of this result could be as follows: parenteral administration of apomorphine produces an increase in locomotion by its binding to dopaminergic receptors located in several brain structures related to motor activity. By lesioning the Acc with ibotenic acid, the number of dopaminergic receptors available for binding to apomorphine is reduced, and consequently, a decrease in locomotion ensues.

Finally, when electrolytic lesion was performed, the behaviors elicited by amphetamine did not experiment any change. However, with apomorphine administration, an increase in three types of stereotypies was observed (head movements, head shaking, and limb shaking). In this type of lesion, in which cells and fibers are damaged, the results can be explained by the motor inhibitory hypothesis (12,14). However, another possibility must be taken into consideration: the electrolytic damage according to Taghzouti et al. (25) also will lesion dopaminergic passing fibers to the prefrontal cortex, and we have shown in a previous work (7) that the ablation of this structure in cats also increases head shaking, evoked by parenteral administration of apomorphine. Then, in the result obtained by electrolytic lesion of the Acc and apomorphine administration, a possible involvement of the prefrontal cortex should be considered. It is worthy to comment on the result of the experimental work reported by Weissenborn and Winn (26). They bilaterally injected N-methyl-D-aspartate (NMDA) into the Acc in a group of rats and compared the behaviors produced by this drug with those evoked in another group of rats that received 6-OHDA lesion in both Acc. The observation period lasted 8 weeks postsurgery. NMDA Acc lesions significantly enhanced exploratory behavior, spontaneous locomotor activity, and the locomotor response to a low dose of D-amphetamine. By comparison, 6-OHDA lesions did not affect exploration and spontaneous locomotion, but significantly attenuated the locomotor response to a low dose of amphetamine.

According to the authors the results suggest that NMDA Acc lesions induce a deficit in the control of general locomotor output and are consistent with the hypothesis that the Acc functions as an interface between sensory input and locomotor output. The authors pointed out that on the basis of their results it is not possible to determine whether Acc-DA containing neurons serve as control units for general activity levels, and considering that selective destruction of neurons intrinsic to the Acc does not attenuate D-amphetamine–induced hyperactivity, this result indicates that Acc neurons are not involved in mediating the stimulating effects of the drug.

The results of Weissenborn and Winn experiments (26) corroborated the involvement of Acc in locomotor activity in rats, reported by previous work (2–4). Their final comment that Acc neurons are not involved in mediating the stimulatory effect of amphetamine agrees with our data and point of view that when injecting parenterally dopaminergic agonist drugs, other structures besides the Acc become involved in the production of behaviors. However, a comparison of their results with ours has a limited value, due to the fact that the two works were performed in two different animal species, and, as cited previously, amphetamine in cats evoked immobility, while in rats it evoked increased locomotion. Also, the stereotypies behaviors in rats are different from those observed in cats.

The results observed in the present work about Acc functions deserves some comments. The Acc involvement in locomotor activities in the cat is demostrated, but it does not seem as important as described by various researchers in rodents (1,3–5,11,12). The passing dopaminergic fibers to the prefrontal cortex could also be damaged, and it is difficult to discriminate about the involvement of each of these structures in the analyzed motor activity. Another important fact to be taken into account is the interconnection of the Acc with structures that also receive dopaminergic fibers, and the demonstration by Simon et el. (23), that the damage of one structure that receives dopaminergic innervation can be accompanied by an increase in DA release by other structures.

The motor involvement of the Acc is related not only to locomotion, but also to stereotyped behaviors, like head shaking, limb shaking, and head movements. On the other hand, the present work shows the relationship of the Acc with emotional behaviors like fear, explained by the interconnections of the Acc with other structures of the limbic system like the amygdala (2).

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