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Behavioral Effects of Amphetamine and Apomorphine After Striatal Lesions in the Rat

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ANTONIOU, K. AND E. KAFETZOPOULOS. *Behavioral effects of amphetamine and apomorphine after striatal lesions in the rat.* PHARMACOL BIOCHEM BEHAV 43(3) 705–722, 1992.—It is well established that denervation of the dorsal striatum by its dopaminergic afferents attenuates the stereotyped response to *d*-amphetamine, which can be considered as an extreme form of motor activation. However, it is difficult to sustain the view that this structure serves primary motor control function because the role of dopamine in the striatum remains difficult to understand. In this study, we compared the effects of two dopaminergic agonists, *d*-amphetamine and apomorphine, after dorsal striatal lesions with ibotenic acid using a computerized scoring of the behavior. Although *d*-amphetamine- and apomorphine-induced locomotor activity was no different between lesioned and nonlesioned rats in photobeam activity cages, the structure of their behavioral pattern was quite different. Freezing, a usual response after *d*-amphetamine, was blocked by the lesion. Lesioned rats exhibited less standing than nonlesioned after *d*-amphetamine, apomorphine, or saline treatment. Moving was increased in lesioned rats after a low dose of *d*-amphetamine (0.5 mg/kg) or apomorphine (0.5 mg/kg), while *d*-amphetamine induced in the same rats an increase of rearing. Stereotyped behavior after both drugs at high doses was not affected by striatal lesion. These results indicate that the dorsal striatum is not involved only in the control of stereotypy, as has been suggested using 6-hydroxydopamine lesions, but also plays a major role in the mediation of behavioral activation in response to stimulant drugs.

Amphetamine Apomorphine Open field Motor activity Ibotenic acid Corpus striatum Rats

THE neurochemical and behavioral effects of two drugs, *d*-amphetamine (*d*-AMPH) and apomorphine (APO), have been the focus of research for several decades (7,33,40,45). Because their primary action is stimulation of the dopaminergic system, their study may help to elucidate this system (48). *d*-AMPH acts as an indirect dopaminergic agonist by enhancing the amount of neurotransmitter release (4,6,20) and blocking its reuptake (11,15) while APO, as a direct agonist, acts via pre- and postsynaptic dopaminergic receptors (2,7).

Both drugs exert a well-known effect on spontaneous motor behavioral elements that is usually referred to as hyperactivity. By increasing the dose, the hyperactivity is replaced by stereotyped behavior (5,7,27,44,45). According to current views, this behavioral syndrome is mediated through the dopaminergic activity in the mesolimbocortical and nigrostriatal systems (22,28–30). It has also been suggested that *d*-AMPH-induced locomotor activation is mediated by an increase in dopamine (DA) neurotransmission in the nucleus accumbens because 6-hydroxydopamine (6-OHDA) lesions of the nucleus accumbens (NAS) abolish the stimulant action of *d*-AMPH on locomotor activity (23,28,30).

The corpus striatum (CP) is a major component of the basal ganglia and one of its best demonstrated functions in animal experiments has been the mediation of a behavioral activation characterized by stereotypy after high doses of DA agonists. The elucidation of this function has been based upon a large body of data concerning drug effects after 6-OHDA lesions of the DA terminals projecting to the striatum. Thus, bilateral injection of 6-OHDA into the striatum has been reported to block *d*-AMPH stereotypy (22,30), indicating that the CP plays a major role in amphetamine-induced stereotypy, in contrast to the NAS, which seems to mediate amphetamine-induced locomotor activation.

In a detailed study, however, Fink and Smith (17,18) reported that 6-OHDA lesions induced by infusion of 6-OHDA into the dopaminergic axons in the anterolateral hypothalamus (ALH) or into various dopaminergic terminal fields in the anterior forebrain and verified by fluorescent histochemical analysis failed to reproduce the above findings. They suggested a "mass action" relationship between dopaminergic terminal fields in the anterior forebrain and the locomotor response to *d*-AMPH. Therefore, a large area of denervation is apparently required to abolish the locomotor response but not specific denervated dopaminergic fields, for example, the nucleus accumbens alone. The same authors proposed that dopaminergic innervation of the anterior striatum may also be important for the locomotor response to *d*-AMPH, while the relationship between the same structures and response to

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APO appears to be more complex. In a more recent study, however, Winn and Robbins (51) reported that locomotor and stereotyped responses to *d*-AMPH were abolished after 6-OHDA infusions into the ALH but were enhanced after APO treatment. In addition, 6-OHDA lesions into the nucleus accumbens decreased locomotion in response to 1.5 mg/kg *d*-AMPH but increased locomotion following 0.1 mg/kg APO, while stereotyped responses to larger doses were unaltered. In contrast to Fink and Smith (17,18), Winn and Robbins reported a loss of DA after lesions at the level of ALH not only in the nucleus accumbens and frontal cortex but also in the striatum. On the other hand, they supported another suggestion of Fink and Smith (17,18): A more effective blockage of locomotor response to 1.5 mg/kg *d*-AMPH is produced by additional depletion of DA in the anterior striatum. Further evidence against the view that the NAS and CP might mediate different aspects of DA-related behavior and cautioning that the distinction between locomotor activation and stereotypy is not complete is provided by Costall and Naylor (10); they pointed out that it is possible to produce hyperactivity with intrastriatal injections of DA (9) and, conversely, to produce stereotypy with intraaccumbens injections of DA agonists. Therefore, it seems that the functional distinction between the limbic and striatal DA systems remains in question (3,42).

Although 6-OHDA lesions or drug infusions have been used for years as a tool for the investigation of striatal function and drug effects, some authors have used cytotoxic agents for the same purpose. Striatal kainic acid lesions have been reported to enhance the locomotor and stereotyped responses to *d*-AMPH without affecting the responses to APO (34,35). Kainic acid lesions of the striatum, however, seem to interfere with two major problems: Some of the above authors observed moderate extrastriatal neuronal loss (35,43,47). On the other hand, inspection of the histology figures of Mason et al. (35) reveals that the anteromedial aspects of the striatum were spared by kainic acid injections. The same histological figure is presented by Köhler and Scwarcz (31) in a study comparing the histological effects of ibotenic and kainic acid, indicating that this striatal area may be resistant to kainic acid but not ibotenic acid injections. Despite these problems, however, the striatal lesions are not without effects or impairments, indicating that the striatum probably has a complex function, as has been implicated for a long time (13).

The purpose of the present study was to evaluate and functionally interpret the behavioral effects of two dopaminergic agonists in rats that had received injections of ibotenic acid in the dorsal and medial aspects of the anterior striatum to achieve well-shaped lesions without extrastriatal damage. In this study, a computerized technique for analyzing animal behavior has been developed that provides more information about the behavioral profile than a mere measure of the general activity based upon line crosses or photobeam interruptions. Furthermore, the direct observation provides an accuracy in the determination of the behavioral responses by recording various components of the behavioral activation and is usually preferable in behavioral experiments (16,26,46).

METHOD

Subjects

Male Wistar rats, inbred in the Animal Center of the University of Ioannina and originating from the Institute of Experimental Biology and Medicine (Borstel, Hamburg), weighing 250–300 g, were used throughout the experiment. Rats were housed in groups of four in plastic cages with food and water freely available under controlled illumination and temperature.

Lesion Procedure

Rats were anesthetized with pentobarbital sodium (40 mg/kg, IP), placed in a stereotaxic frame (David Kopf Instruments, Tujunga, CA), and injected bilaterally into the striatum with 10 μg ibotenic acid (Sigma Chemical Co., St. Louis, MO) in 1 μl phosphate buffer (pH 7.4) by lowering the sharpened tip of a 5-μl Hamilton syringe at the following coordinates (41): AP +0.2 mm from bregma, L +2.5 mm from midline, and V +4 mm from the skull surface. Injections were made over a period of 5 min and the injection needle was left in place for a further period of 5 min to minimize leakage of ibotenic acid up the needle track. Sham-operated control animals received injections of vehicle (buffer) alone.

Drugs

Drugs used in the experiment were *d*-AMPH sulfate and APO HCl (Sigma). All rats received only one drug treatment. Rats were injected IP with 0 (vehicle only), 0.5, 1.5, 3, and 6 mg/kg *d*-AMPH and 0 (vehicle only), 0.25, 0.5, 1, and 2 mg/kg APO. Drugs were dissolved in 0.9% saline and in the case of apomorphine 1 mg/kg ascorbic acid was added as an antioxidant. Solutions were freshly prepared immediately prior to use. Groups of 7–10 rats were used for each drug dose.

Apparatus

The activity cage was a transparent plastic cage (40 × 40 × 40 cm) in a room where illumination was low from 8:00 a.m.–5:00 p.m. The activity cage was equipped with four photocells activated by infrared beams (two in each side) and connected to an electronic event recorder. A white noise background was used to help screen out incidental noises during the testing.

Behavioral Testing

Animals were allowed 3 weeks recovery prior to testing in the activity cage. Rats were habituated in the test apparatus for 30 min, then injected with *d*-AMPH, APO, or saline, and reintroduced immediately into the testing cage. Behavior was recorded for 1 h, starting 15 min after *d*-AMPH injection or immediately after APO injection. The 1-h session was divided into three 20-min intervals and each rat was observed for the first 10 min of every 20-min interval. During the 1-h session, cumulative counts of interruptions of the four photobeams were continuously recorded.

The behavior was analyzed by continuously monitoring animals using a technique for quantification of behavioral sequences modified after Spruijt and Gispen (49). In brief, behavior was recorded through a videocamera by one observer using a microcomputer for data storage. A number of the keys of the computer keyboard represented the behavioral elements being tested. With the touch of a key, the system clock was read and the time was stored as duration of this behavioral element. The program stored sequences of behavioral elements and their concomitantly registered time points for every 10-min observation period. The same program via a subsequent automatic analysis of the data provided the total frequency, duration, and mean duration of every element in the 10-min interval.

The behavior was noted to represent the following ele-

ments: standing (std), moving (mov), sniffing (sni), grooming (grm), rearing (rr), scratching (scr), freezing (frz), yawning (yaw), sniffing air (sna), head-swinging (hsw), licking (lck), and gnawing (gnw). Only one of these elements (the most prominent) was scored using the keyboard. Usually, only one behavioral element was exhibited, but occasionally an animal might simultaneously exhibit two. This occurred most often with sniffing, which interfered with moving, rearing, or standing. In these cases, to facilitate scoring the most prominent element was scored according to the following rules:

- std. The rat was on its four feet, essentially motionless, not moving, and not actively sniffing.
- mov. The rat was walking on four feet. Sometimes, the rat was moving while sniffing the air or the apparatus, and in this case was considered minimal and moving was scored.
- sni. The rat was not moving and was smelling any part of the apparatus.
- grm. The rat was washing its face or any other part of its body, and generally its mouth was touching its body.
- rr. The rat's body was inclined vertically with its hindpaws on the floor of the activity cage and the forepaws on the wall of the cage. Sometimes, the rat was rearing while sniffing, and in this case sniffing was considered minimal and rearing was scored.
- scr. The rat was rising its hindpaw against its body.
- frz. The rat was standing on its four feet in a freezing position completely inactive.
- yaw. The rat was standing on its four feet and yawning.
- sna. The rat was rearing but its forepaws were not touching any part of the activity cage.
- hsw. The rat was standing on four feet and moving its head horizontally.
- lck. The rat was standing and licking any part of the apparatus.
- gnw. The rat was standing and was trying to gnaw any part of the apparatus.

Histology

At the end of the testing, 30 days after the lesion, a routine histological analysis was performed to verify the site and extent of the lesions. Rats were killed using an overdose of pentothal, and after intracardial perfusion with formalin brains were removed and fixed in a formalin–sucrose solution for 4 days. Coronal sections, cut at 30 μm in a cryostat, were stained with toluidine blue. The extent of the lesions was verified under microscopic examination and transferred visually onto the corresponding plates of the Paxinos and Watson atlas (41) (Fig. 6).

Statistical Analysis

The data for the photocell beam interruptions and the behavioral measures for each behavioral element tested are shown in detail in Fig. 1–5. A two-way analysis of variance (ANOVA) was used with lesion and dose as factors for each drug (*d*-AMPH, APO) while a one-way ANOVA was used with lesion as the factor on the effects after saline treatment. A separate one-way ANOVA was performed on the effects of *d*-AMPH and APO, with dose as the factor for lesioned rats. Scheffe's multiple-range tests followed each ANOVA for systematic comparison of the means between the groups (Tables 1, 2A, and 2B). Independent Student's *t*-tests were performed to investigate differences between each drug dose in lesioned and sham-operated rats for each behavioral measure (Table 3).

RESULTS

d-AMPH Effects

Photocell beam interruptions: The two-way ANOVA with lesion and dose as factors revealed a significant dose effect, $F(1, 3) = 32.009$, $p < 0.001$. The one way ANOVA with dose as factor for lesioned and sham-operated rats revealed a significant dose effect [$F(3,26) = 20.79$, $p < 0.001$, and $F(3, 37) = 17.05$, $p < 0.001$, respectively]. The subsequent multiple-range tests showed that the highest score of interruptions was at 1.5 mg/kg after *d*-AMPH treatment ($p < 0.05$) (AMPH 0 mg/kg = 209, AMPH 0.5 mg/kg = 653, AMPH 1.5 mg/kg = 1,559, AMPH 3 mg/kg = 908) in lesioned rats, while in sham-operated rats the highest score was at the highest dose ($p < 0.05$) (AMPH 0 mg/kg = 129, AMPH 0.5 mg/kg = 613, AMPH 1.5 mg/kg = 1,285, AMPH 3 mg/kg = 1,469). Students' *t*-tests revealed that lesioned rats had fewer interruptions than sham-operated rats at 3 mg/kg *d*-AMPH (Table 3).

Standing. The two-way ANOVA with lesion and dose as factors revealed a significant lesion effect on frequency, $F(1, 4) = 45.86$, $p < 0.001$, and duration, $F(1, 4) = 35.87$, $p < 0.001$, and a significant dose effect on frequency, duration, and mean duration [$F(1, 4) = 19.9$, $p < 0.001$, $F(1, 4) = 82.15$, $p < 0.001$, and $F(1, 4) = 19.64$, $p < 0.001$, respectively]. Scheffe's multiple-range tests revealed that lesioned rats exhibited a lower frequency and shorter duration of standing than sham-operated rats (Table 1). Independent Student's *t*-tests between lesioned and sham-operated rats revealed that lesioned rats were standing less and more rarely than sham-operated rats, except at the higher dose (Table 3).

The separate one-way ANOVA with dose as factor only for lesioned rats revealed a significant dose effect on frequency, $F(4, 33) = 7.2$, $p < 0.001$, duration, $F(4, 33) = 258$, $p < 0.001$, and mean duration, $F(4, 33) = 12.5$, $p < 0.001$, and subsequent-multiple range tests showed statistical differences between the lower doses and the higher doses on frequency, duration, and mean duration (Table 2.1).

Moving. The two-way ANOVA with lesion and dose as factors revealed a significant dose effect on frequency, duration, and mean duration [$F(1, 4) = 28.44$, $p < 0.001$, $F(1, 4) = 18.94$, $p < 0.001$, and $F(1, 4) = 6.61$, $p < 0.001$, respectively]. Student's *t*-tests revealed that lesioned rats were moving more than sham-operated rats at 0.5 mg/kg *d*-AMPH (Table 3).

The separate-one way ANOVA for lesioned rats with dose as factor revealed a significant dose effect on frequency, $F(4, 33) = 21.36$, $p < 0.001$, and duration of moving, $F(4,33) = 7.06$, $p < 0.001$. Multiple-range tests showed that lesioned rats were moving more at 1.5 mg/kg *d*-AMPH and more frequently at every dose (except at the highest dose) compared to saline (0) group (Table 2.1).

Sniffing. The two-way ANOVA with lesion and dose as factors revealed a significant dose effect on the frequency, $F(1, 4) = 16.28$, $p < 0.001$, duration, $F(1, 4) = 12,42$, $p < 0.001$, and mean duration, $F(1, 4) = 6.65$, $p < 0.001$. Student's *t*-tests revealed that lesioned rats exhibited more sniffing episodes than sham-operated rats at 6 mg/kg *d*-AMPH (Table 3).

The separate one-way ANOVA with dose as factor only for lesioned rats revealed a significant dose effect on frequency, $F(4, 33) = 9.33$, $p < 0.001$, duration, $F(4, 33) = 4.24$, $p < 0.01$, and mean duration of sniffing, $F(4, 33) = 2.6$, $p < 0.05$. Subsequent Scheffe's multiple-range tests showed more sniffing episodes between every dose and the

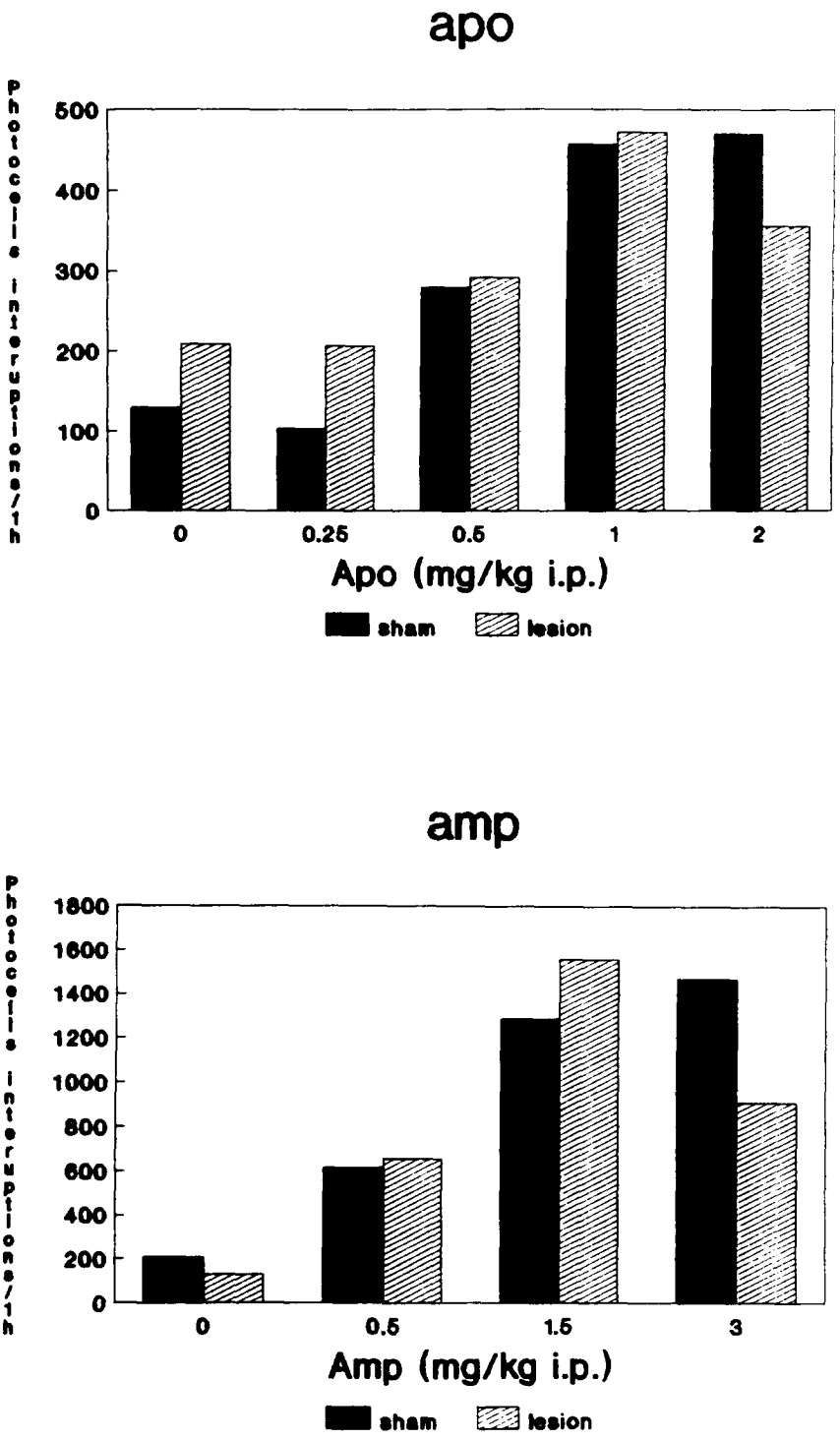

FIG. 1. Effects of saline (dose 0), *d*-AMPH (amp), and APO (apo) on the photobeam interruptions in lesioned and sham-operated rats in a continuous 1-h recording session in a 40 × 40 × 40-cm open field.

saline (0) (except for the highest dose of *d*-AMPH) and longer duration of sniffing at 0.5 and 3 mg/kg *d*-AMPH.

Grooming. The two-way ANOVA with lesion and dose as factors revealed a significant dose effect on frequency, $F(1, 4) = 7.11$, $p < 0.001$, and duration, $F(1, 4) = 11.04$, $p < 0.001$. Scheffe's multiple-range tests showed that sham-operated rats exhibited more grooming episodes (Table 1).

The separate one-way ANOVA with dose as factor for

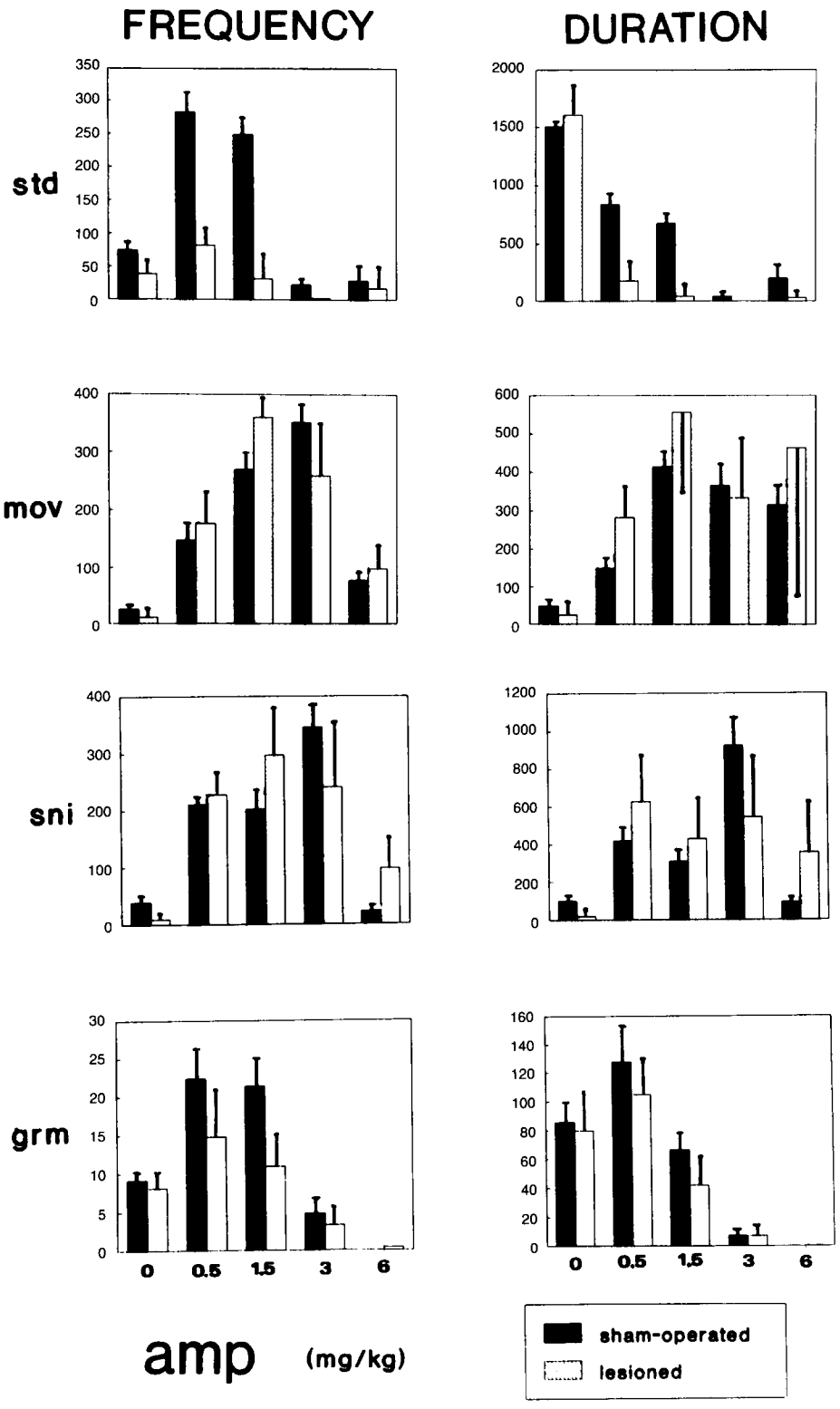

FIG. 2. Effects of *d*-AMPH (amp) on the frequency and duration of behavioral elements in lesioned and sham-operated rats. For each element, the cumulative frequency scores of three 10-min recording sessions separated by 10-min intervals or the total duration in seconds of the three 10-min recording sessions are plotted and arranged horizontally according to the dose of the drug (dose 0: saline). std, standing; mov, moving; sni, sniffing; grm, grooming; rr, rearing; scr, scratching; yaw, yawning; frz, freezing; sna, sniffing air; hsw, head-swinging; lck, locking; gnw, gnawning.

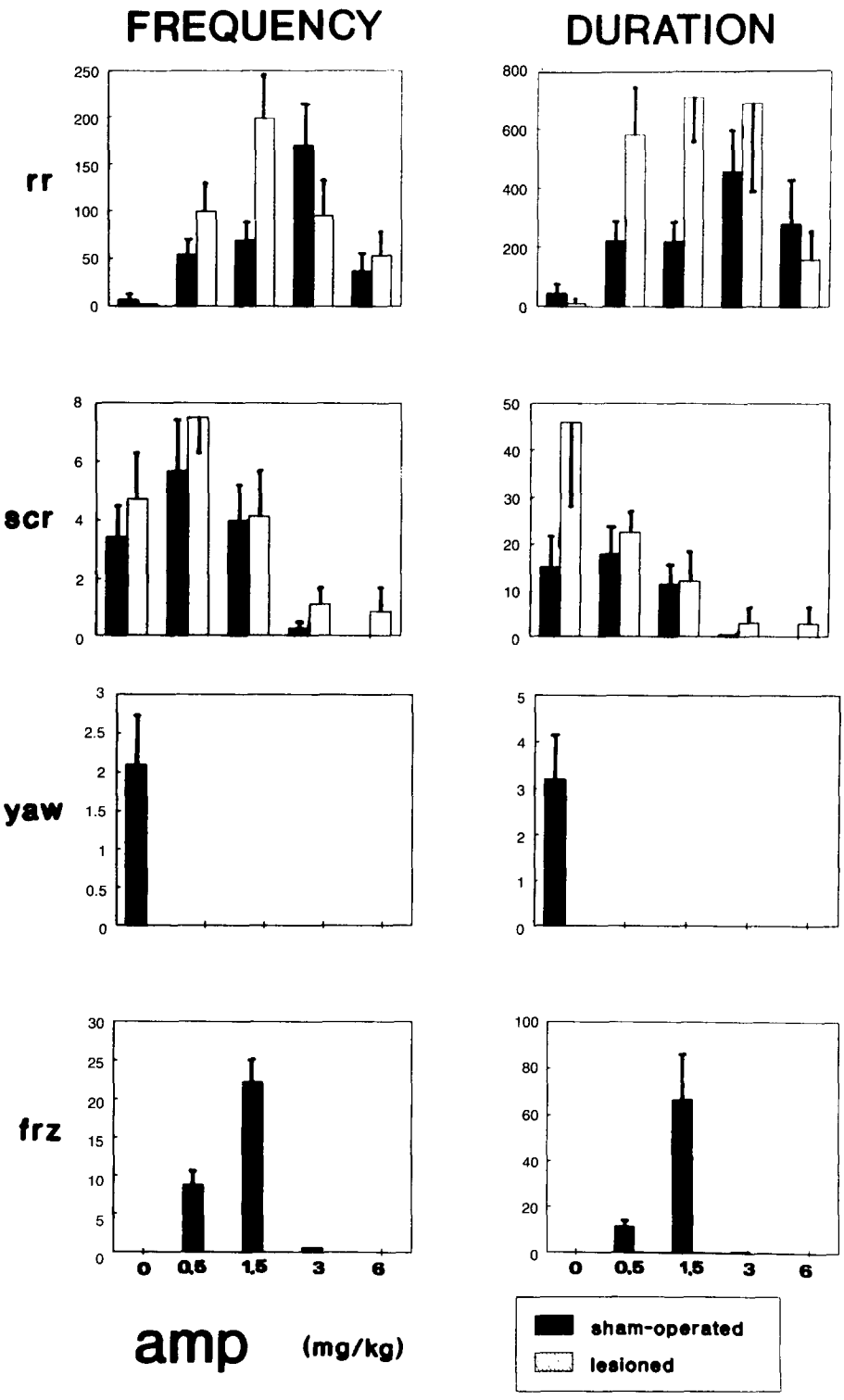

FIG. 2. *continued.*

lesioned rats revealed a significant dose effect on frequency, $F(4, 3) = 4.53$, $p < 0.01$, and duration of grooming, $F(4, 33) = 4.96$, $p < 0.001$. Scheffe's multiple-range tests showed that by increasing the dose of *d*-AMPH there was a decrease in the frequency and duration of grooming in lesioned rats (Table 2.1).

Rearing. The two-way ANOVA with lesion and dose as factors revealed a significant lesion effect on frequency, $F(1,$

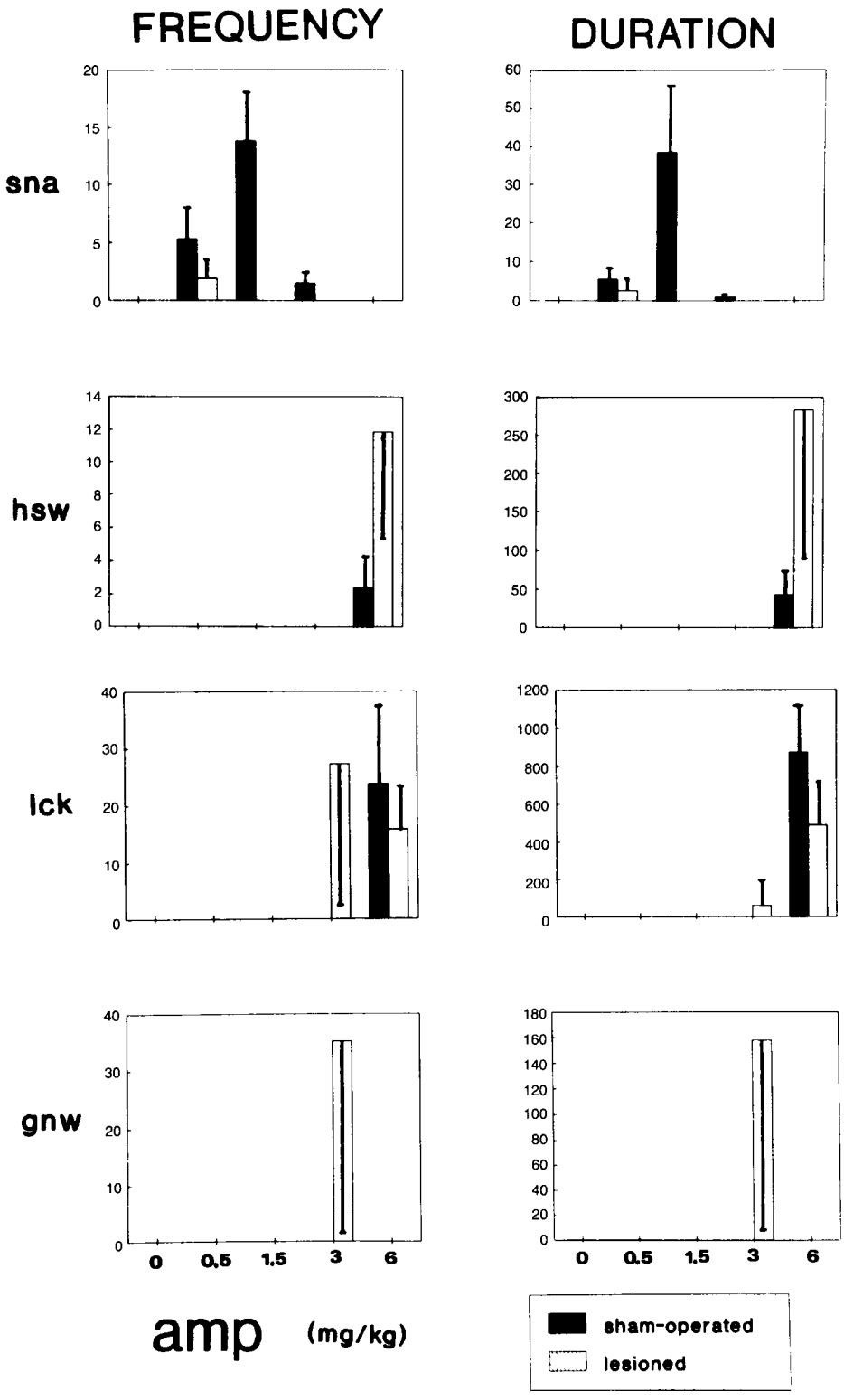

FIG. 2. *continued.*

4) = 4.15, $p < 0.05$, and duration, $F(1, 4) = 10.79$, $p < 0.001$, as well as a significant dose effect on frequency, $F(1, 4) = 7.27$, $p < 0.001$, and duration, $F(1, 4) = 5.77$, $p < 0.001$. Multiple-range tests showed lesion induced an increase in the frequency and duration of rearing (Table 1). Student's *t*-tests revealed that lesioned rats exhibited a longer duration of rearing at 0.5 and 1.5 mg/kg and a higher frequency at 1.5 mg/kg *d*-AMPH compared to sham-operated rats. (Table 3).

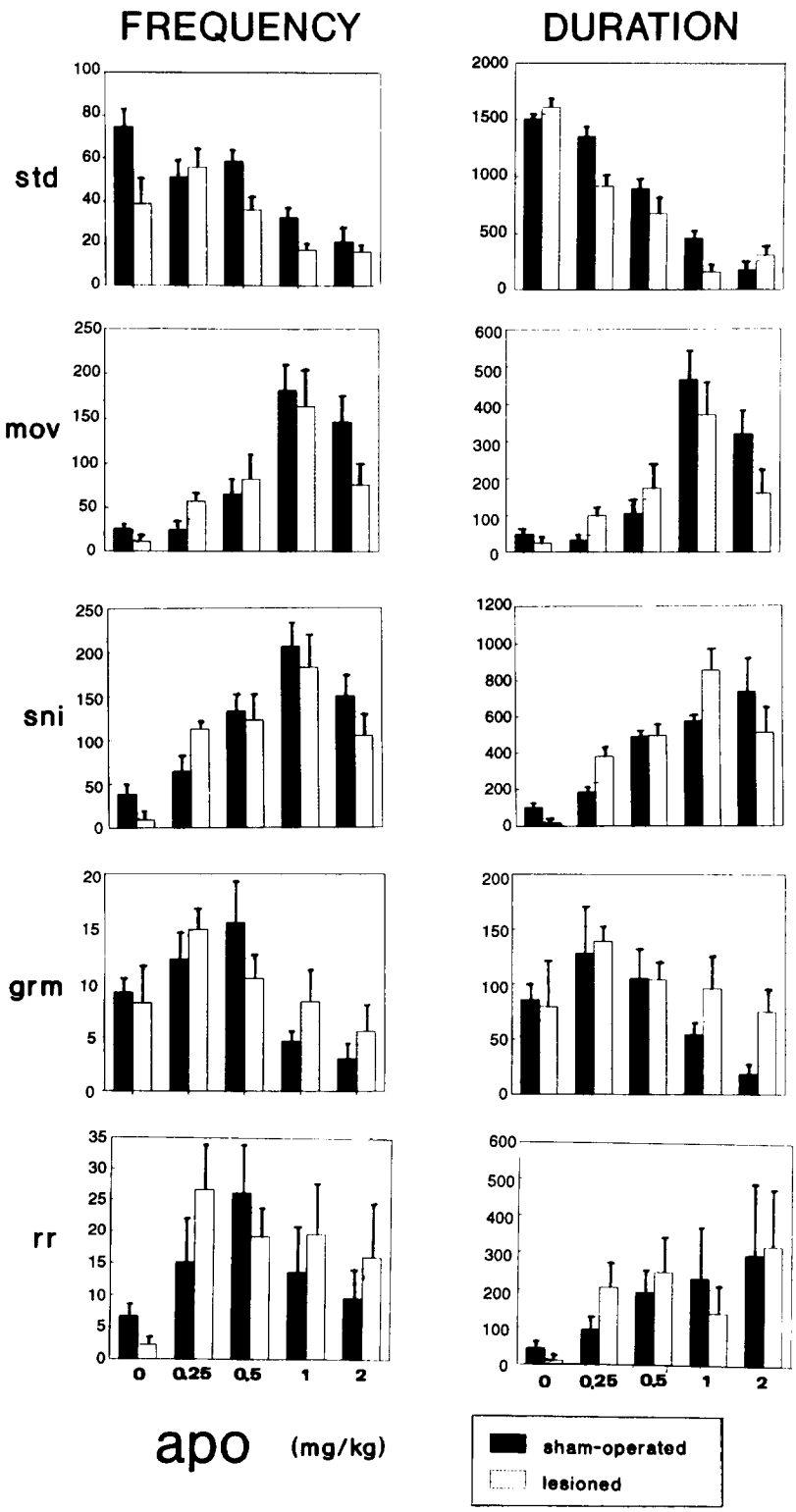

FIG. 3. Effects of APO (apo) on the frequency and duration of behavioral elements in lesioned and sham-operated rats. For each element, the cumulative frequency scores of three 10-min recording sessions separated by 10-min intervals or the total duration in seconds of the three 10-min recording sessions are plotted and arranged horizontally according to the dose of the drug (dose 0: saline). Abbreviations as in Fig. 2.

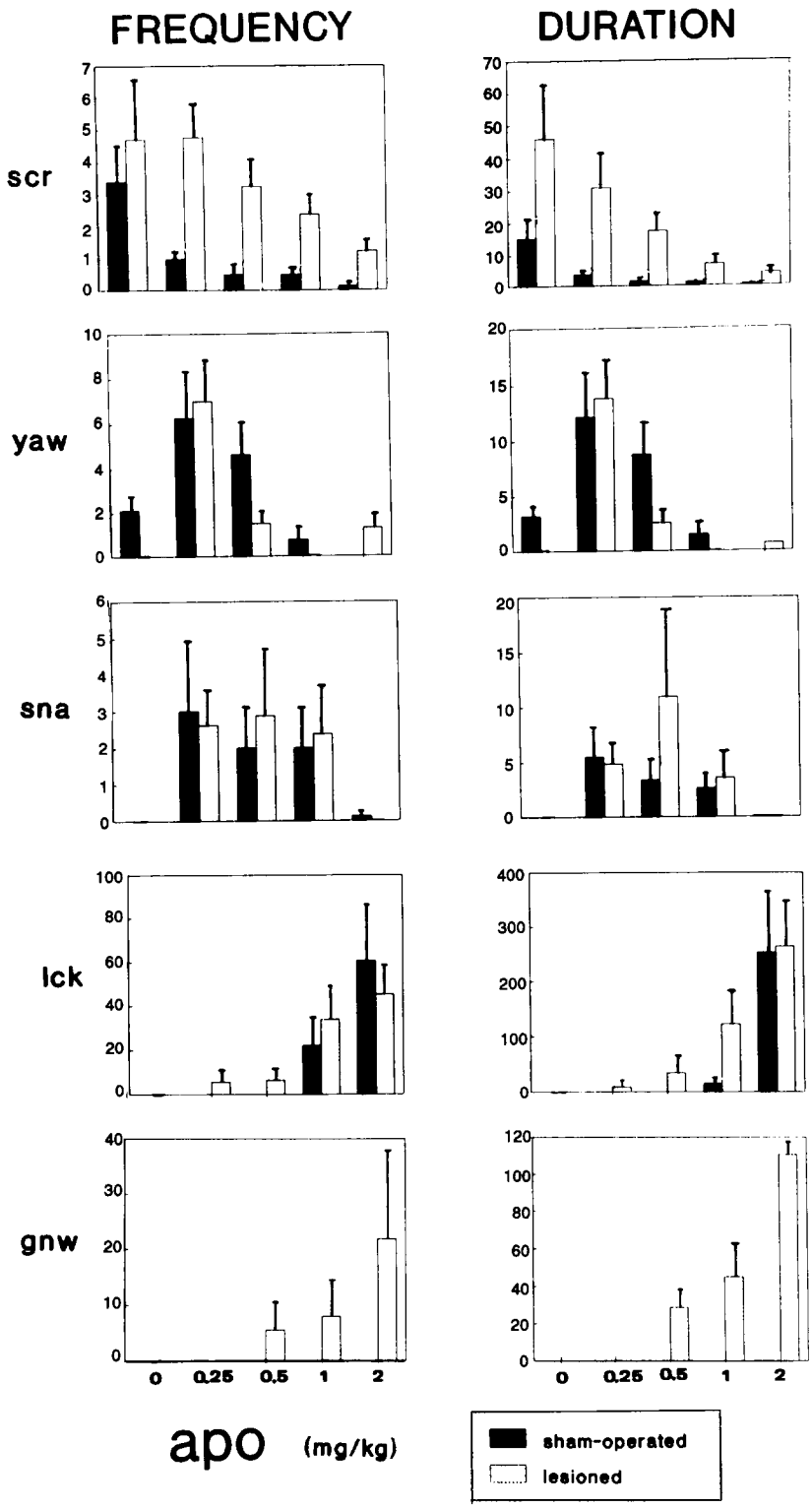

FIG. 3. *continued.*

The separate one-way ANOVA with dose as factor for lesioned rats revealed a significant dose effect on frequency, $F(4, 33) = 7.38$, $p < 0.001$, and duration of rearing, $F(4, 33) = 4.94$, $p < 0.001$, and multiple-range tests showed that by increasing the dose of *d*-AMPH there was a decrease in the frequency and duration in lesioned rats (Table 2.1).

Scratching. The two-way ANOVA with lesion and dose as factors revealed a significant dose effect on frequency,

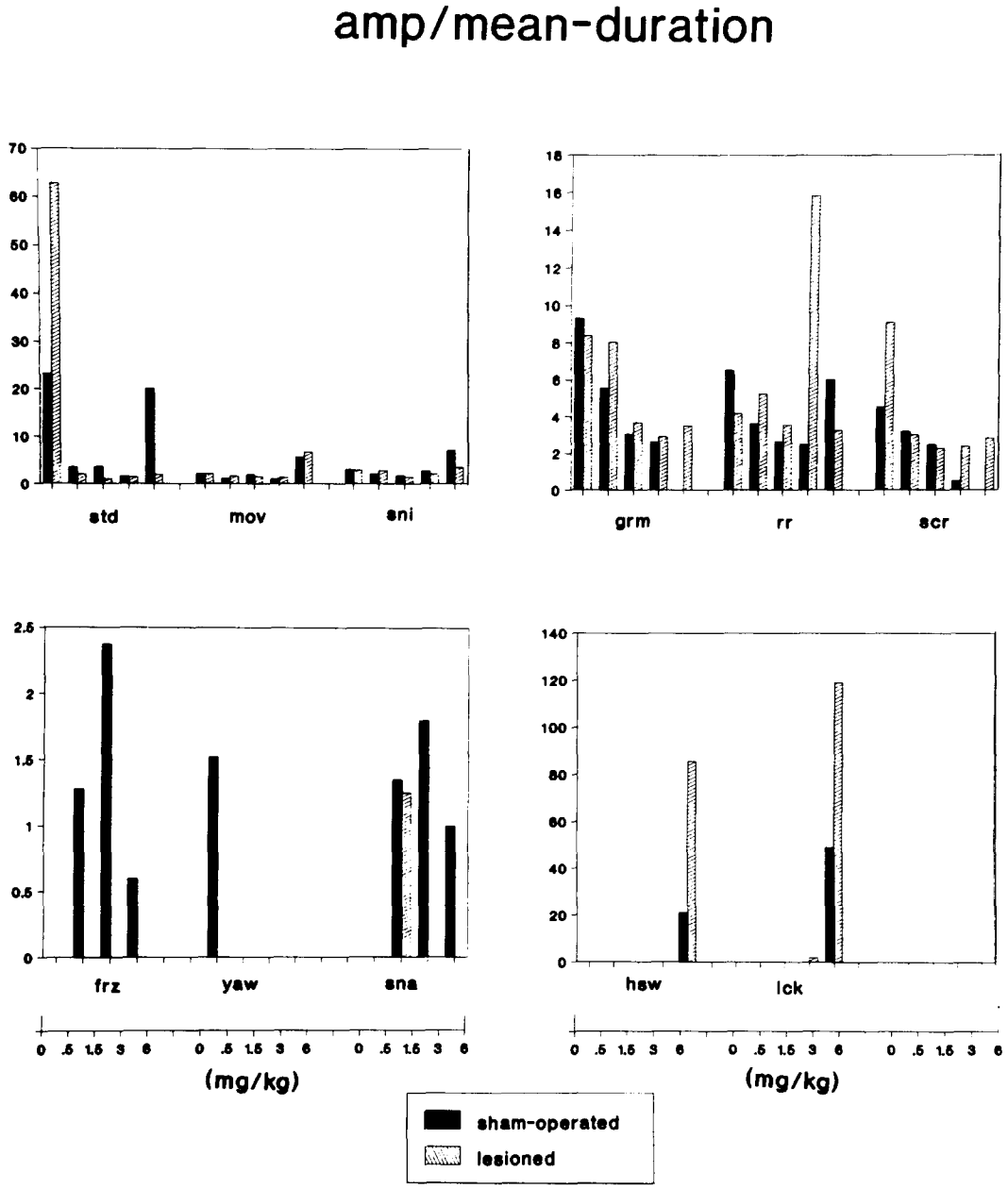

FIG. 4. Effects of four doses of *d*-AMPH (amp) and saline (dose 0) on the mean duration (duration/frequency) of behavioral elements in lesioned and sham-operated rats. Abbreviations as in Fig. 2.

$F(1, 4) = 4.5$, $p < 0.05$, and duration, $F(1, 4) = 5.23$, $p < 0.001$.

The separate one-way ANOVA with dose as factor for lesioned rats revealed a significant dose effect on frequency, $F(4, 33) = 4.21$, $p < 0.01$, duration, $F(4, 33) = 4.86$, $p < 0.001$, and mean duration, $F(4, 33) = 3.03$, $p < 0.04$, and multiple-range tests showed that by increasing the dose there was a decrease in frequency and duration of scratching in lesioned rats (Table 2.1).

Freezing. The two-way ANOVA with lesion and dose as factors revealed a significant lesion effect on frequency, $F(1, 4) = 21.46$, $p < 0.001$, and duration, $F(1, 4) = 3.63$, $p < 0.05$, as well as a significant dose effect on frequency, $F(1, 4) = 14.69$, $p < 0.001$, and duration, $F(1, 4) = 3.93$, $p < 0.05$. Scheffe's multiple-range tests showed that lesion abolished freezing (Table 1). Independent Student's *t*-tests revealed a great decrease in frequency and duration of freezing in lesioned compared to sham-operated rats (Table 3).

Sniffing air. The two-way ANOVA with lesion and dose as factors revealed a significant dose effect on frequency, $F(1, 4) = 2.51$, $p < 0.05$. Scheffe's multiple-range tests showed an increase in frequency of sniffing air in lesioned compared to sham-operated rats (Table 1).

Head-swinging. The two-way ANOVA with lesion and

dose as factors revealed a significant dose effect on frequency, $F(1, 4) = 8.98$, $p < 0.001$, and duration, $F(1, 4) = 6.41$, $p < 0.001$. There was also an increase in frequency and duration of head-swinging in lesioned compared to sham-operated rats, but this increase did not reach any statistical significance (Fig. 2C).

Licking. The two-way ANOVA with lesion and dose as factors revealed a significant dose effect on frequency, $F(1, 4) = 2.66$, $p < 0.05$, and duration, $F(1, 4) = 32.95$, $p < 0.001$.

The separate one-way ANOVA with dose as factor only for lesioned rats revealed a significant dose effect on duration, $F(4, 33) = 8.2$, $p < 0.001$. Scheffe's multiple-range tests showed a great increase in duration of licking at the highest dose of *d*-AMPH in lesioned rats (Table 2.1).

Gnawing. The results showed an increase in frequency and duration of gnawing at high doses of *d*-AMPH in lesioned rats but this increase did not reach any statistical significance (Fig. 2C).

In general, lesioned rats were standing less after *d*-AMPH than sham-operated rats. Lesioned rats showed an increase in moving at the lowest dose and an increase in sniffing at the highest dose. There was an increase in rearing in lesioned compared to sham-operated rats, while freezing was not exhibited in lesioned rats. In addition, a tendency for increased stereotypy behavior was observed in lesioned rats.

APO Effects

Photocell beam interruptions. The two-way ANOVA with lesion and dose as factors revealed a significant dose effect, $F(1, 4) = 6.66$, $p < 0.001$. Students' *t*-tests did not reveal any significant difference in photocell interruptions between lesioned and sham-operated rats (Table 3). The one-way ANOVA with dose as factor only for lesioned rats did not reveal any significant effect. In contrast, the same ANOVA for sham-operated rats revealed a significant dose effect, $F(4, 31) = 6.24$, $p < 0.001$. The subsequent multiple-range tests revealed a decrease in interruptions at the lowest dose of APO treatment ($p < 0.05$) (APO 0 mg/kg = 129, APO 0.25 mg/

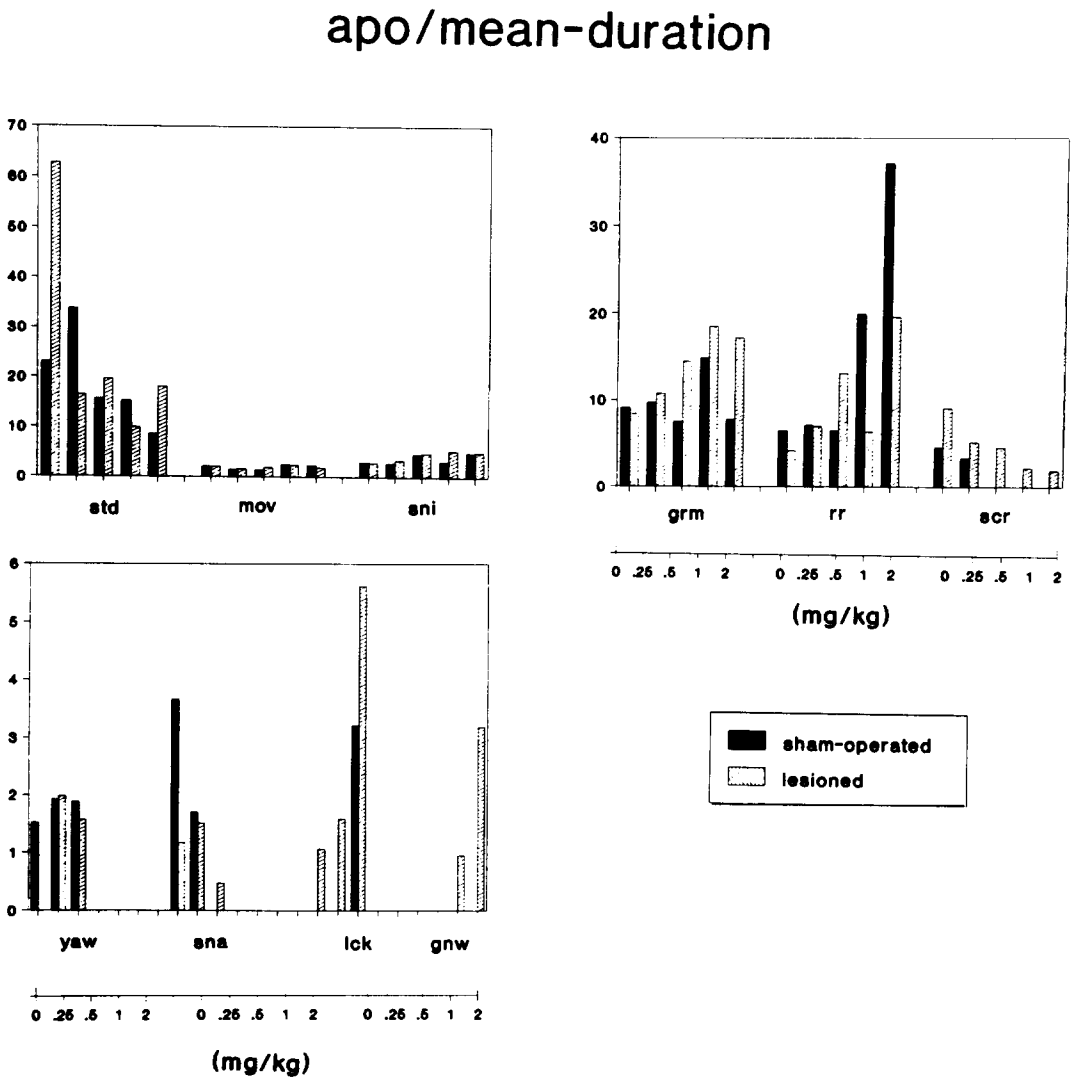

FIG. 5. Effects of four doses of APO (apo) and saline (dose 0) on the mean duration (duration/frequency) of behavioral elements in lesioned and sham-operated rats. Abbreviations as in Fig. 2.

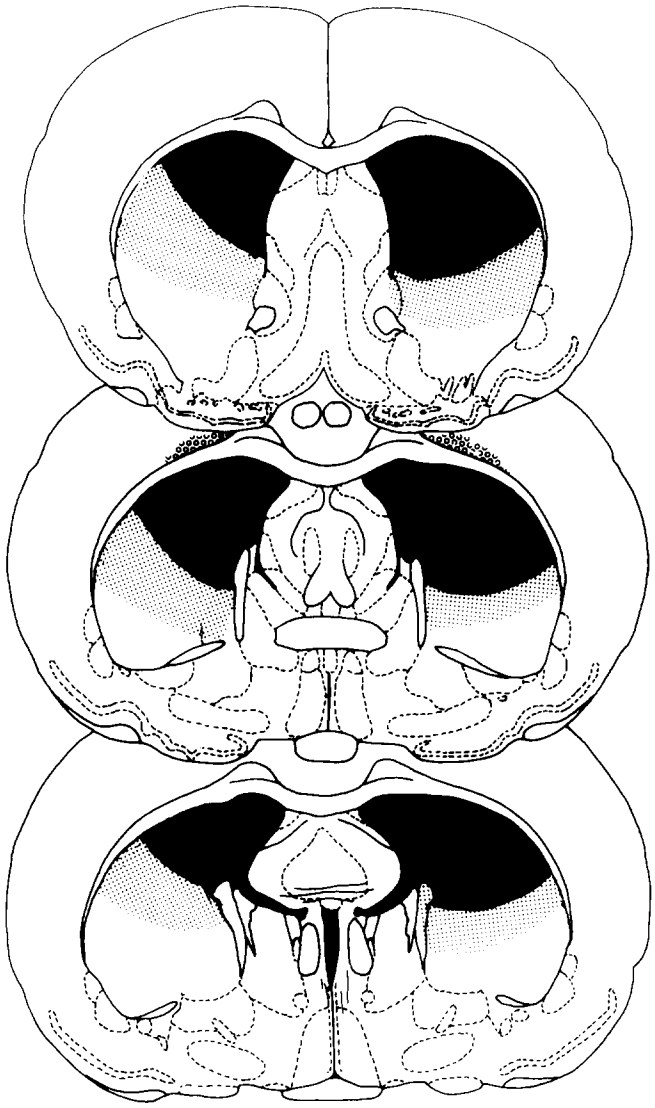

FIG. 6. Serial sections showing the localization and extent of the ibotenic acid lesions of the neostriatum as seen upon light microscopy and transferred visually on the corresponding diagrams from Paxinos and Watson's atlas (41). The black area represents the smallest lesion and the gray area the biggest, the limits of the remaining lesions lying roughly between them.

kg = 103, APO 0.5 mg/kg = 280, APO 1 mg/kg = 456, APO 2 mg/kg = 469).

Standing. The two-way ANOVA with lesion and dose as factors revealed a significant lesion effect on frequency, $F(1, 4) = 11.57$, $p < 0.001$, and duration, $F(1, 4) = 7.45$, $p < 0.05$, as well as a significant dose effect on frequency, $F(1, 4) = 13.21$, $p < 0.001$, duration, $F(1, 4) = 90.26$, $p < 0.001$, and mean duration, $F(1, 4) = 6.69$, $p < 0.001$. Multiple-range tests showed a decrease in frequency and duration of standing but an increase in mean duration in lesioned compared to sham-operated rats (Table 1). Students' *t*-tests revealed that lesioned rats were standing less and more rarely than sham-operated rats (Table 3).

The one-way ANOVA with dose as factor for lesioned rats revealed a significant dose effect on frequency, $F(4, 34) = 6.1$, $p < 0.001$, duration, $F(4, 34) = 37.25$, $p < 0.001$, and mean duration, $F(4, 34) = 5.86$, $p < 0.001$, and multiple-range tests revealed a decrease in frequency, duration, and mean duration as the dose of APO was increased (Table 2.2).

Moving. The two-way ANOVA with lesion and dose as factors revealed a significant dose effect on frequency, $F(1, 4) = 12.59$, $p < 0.001$, duration $F(1, 4) = 12.69$, $p < 0.001$, and mean duration, $F(1, 4) = 3.47$, $p < 0.05$. Students' *t*-tests revealed an increase in frequency and duration of moving in lesioned rats at the lowest dose of APO compared to sham-operated rats (Table 3).

The one-way ANOVA with dose as factor for lesioned rats revealed a significant dose effect on frequency, $F(4, 34) = 3.93$, $p < 0.01$, and duration, $F(4, 34) = 4.37$, $p < 0.01$, and multiple-range tests showed an increase in frequency and duration of moving by increasing the dose of APO in lesioned rats (Table 2.2).

Sniffing. The two-way ANOVA with lesion and dose as factors revealed a significant dose effect on frequency, $F(1, 4) = 15.5$, $p < 0.001$, duration, $F(1, 4) = 15.85$, $p < 0.001$, and mean duration, $F(1, 4) = 3.14$, $p < 0.05$. Student's *t*-tests revealed an increase in frequency and duration in lesioned compared to sham-operated rats after the lowest dose of APO (Table 3).

The one-way ANOVA with dose as factor only for lesioned rats revealed a significant dose effect on frequency, $F(4, 34) = 5.86$, $p < 0.001$, and duration, $F(4, 34) = 8.42$, $p = 0.001$, and multiple-range tests showed an increase in frequency and duration of sniffing as the dose was increased (Table 2.2).

Grooming. The two-way ANOVA with lesion and dose as factors revealed a significant dose effect on frequency, $F(1, 4) = 5.39$, $p < 0.001$. Students' *t*-tests showed a significant increase in duration of grooming in lesioned compared to sham-operated rats (Table 3).

Scratching. The two-way ANOVA with lesion and dose as factors revealed a significant lesion effect on frequency, $F(1, 4) = 14.61$, $p < 0.001$, and duration, $F(1, 4) = 15.66$, $p < 0.001$, as well as a significant dose effect on frequency, $F(1, 4) = 4.59$, $p < 0.05$, and duration, $F(1, 4) = 5.5$, $p < 0.05$. Multiple-range tests showed an increase in frequency and duration in lesioned rats (Table 1). Students' *t*-tests showed a higher frequency and a longer duration of scratching in lesioned compared to sham-operated rats (Table 3).

The one-way ANOVA with dose as factor for lesioned rats revealed a significant dose effect on duration of scratching, $F(4, 34) = 3.52$, $p < 0.01$.

Yawning. The two-way ANOVA with lesion and dose as factors revealed a significant dose effect on frequency, $F(1, 4) = 11.35$, $p < 0.001$, and duration, $F(1, 4) = 12.21$, $p < 0.001$.

The one-way ANOVA with dose as factor for lesioned rats revealed a significant dose effect on frequency, $F(4, 34) = 10$, $p < 0.001$, and duration, $F(4, 34) = 10.71$, $p < 0.001$, and multiple-range tests showed a decrease in frequency and duration of yawning as the dose of APO was increased (Table 2.2).

Licking. The two-way ANOVA with lesion and dose as factors revealed a significant dose effect on frequency, $F(1, 4) = 7.77$, $p < 0.001$, and duration, $F(1, 4) = 9.56$, $p < 0.001$.

The one-way ANOVA with dose as factor for lesioned rats revealed a significant dose effect on frequency, $F(4, 34) =$

TABLE 1

GROUP AVERAGES OF FREQUENCY, DURATION, AND MEAN DURATION OF VARIOUS BEHAVIORAL ELEMENTS PRESENTING A STATISTICALLY SIGNIFICANT DIFFERENCE ($p < 0.05$) ON LESION FACTOR (LESIONED vs SHAM-OPERATED) REVEALED BY SCHEFFE'S MULTIPLE-RANGE TESTS FOLLOWING ANOVA WITH DOSE AND LESION AS FACTORS IN *d*-AMPH- AND APO-TREATED RATS

	d-AMPH Effects			APO Effects		
	Frequency	Duration	Mean Duration	Frequency	Duration	Mean Duration
std						
Lesioned	35.28	350.34		32.64	711.1	23.66
Sham operated	182.61	724.31		48.85	906.92	19.45
grm						
Lesioned	7.65					
Sham operated	15.82					
rr						
Lesioned	92.81	449.13				
Sham operated	65.79	226.31				
scr						
Lesioned			2.88	3.23	20.41	
Sham operated			3.11	1.21	4.88	
frz						
Lesioned	0.07	0.15				
Sham operated	10.98	29.2				
sna						
Lesioned	0.57					
Sham operated	6.92					

Nonsignificant group averages between lesioned and sham-operated rats are omitted from the table. std, standing; grm, grooming; rr, rearing; scr, scratching; frz, freezing; sna, sniffing air.

3.77, $p < 0.01$, and duration, $F(4, 34) = 4.7$, $p < 0.001$, and Scheffe's multiple-range tests revealed that the duration of licking increased as the dose was increased (Table 2.2).

Gnawing. The analyses did not reveal any significant effect on frequency, duration, and mean duration of gnawing (Table 2.1). It is worth noting that there was an increase in frequency and duration of gnawing in lesioned rats but this increase did not reach any statistical significance (Fig. 3B).

In general, lesioned rats were standing less after apomorphine than sham-operated rats and were sniffing and moving more at the lowest dose of the drug. An increase in grooming and scratching was observed in lesioned rats. As with *d*-AMPH effects, lesioned rats had a tendency to exhibit increased stereotyped responses.

Saline Effects

Photocell beam interruptions. The one-way ANOVA with lesion as factor did not reveal a significant lesion effect. Students' *t*-tests did not reveal statistical differences between lesioned and sham-operated rats (Table 3).

Standing. The one-way ANOVA with lesion as factor revealed a significant lesion effect on frequency, $F(1, 15) = 6.34$, $p < 0.05$, and mean duration, $F(1, 15) = 5.71$, $p < 0.05$. Student's *t*-tests revealed a significant decrease in frequency but a significant increase in mean duration of standing in lesioned rats (Table 3).

Sniffing. The one-way ANOVA revealed a significant lesion effect on frequency and duration [$F(1, 15) = 4.98$, $p < 0.05$, and $F(1, 15) = 7.19$, $p < 0.01$, respectively]. Students' *t*-tests revealed a significant decrease in frequency and duration in lesioned rats (Table 3).

Rearing. The one-way ANOVA revealed a significant lesion effect on duration, $F(1, 15) = 4.75$, $p < 0.05$. Student's *t*-tests revealed a decrease in duration in lesioned rats (Table 3).

The analyses that were performed did not reveal any statistical difference in frequency, duration, and mean duration of the other behavioral elements tested after saline treatment (Table 3).

DISCUSSION

The present study was primarily concerned with assessing the effects on behavior after various doses of two dopaminergic agonists (*d*-AMPH and APO) in rats with ibotenic acid lesions in the dorsal striatum.

Lesioned rats were standing less after saline treatment, indicating that they were more active than sham-operated rats, but this spontaneous behavioral activation is not related to a motor activation characterized by moving or an exploratory activity characterized by sniffing or rearing. In addition, our results showed that lesioned rats were sniffing and rearing less, exhibiting a lower exploratory activity than sham-operated rats, in agreement with Pisa et al. (43).

d-AMPH administration did not induce any change on the general locomotor activation between lesioned and nonlesioned rats measured by photocell beam interruptions, but significant changes were found by the more detailed analysis of the direct observation-derived data.

At the higher doses of the drug, lesion did not abolish the *d*-AMPH-induced stereotyped behavior, although there was a tendency toward an increase in licking, head-swinging, and gnawing. It is at first sight paradoxical that destruction of cell

TABLE 2A

SCHEFFE'S MULTIPLE-RANGE TESTS ($p < 0.5$) ON GROUP AVERAGES FOLLOWING ANOVA WITH DOSE AS FACTOR ON FREQUENCY, DURATION, AND MEAN DURATION OF BEHAVIORAL ELEMENTS IN *d*-AMPH-TREATED LESIONED RATS

	Frequency		Duration		Mean Duration	
std	3	3.00*	3	4.25*	2	1.01*
	4	17.57*	4	32.57*	3	1.47*
	2	32.50**	2	46.62*	4	1.89*
	0	38.85**	1	178.62*	1	2.04*
	1	82.75*	0	1607.00*	0	55.04*
mov	0	11.71*	0	25.00*		
	4	93.57**	1	282.62**		
	1	177.12**	4	292.85**		
	3	259.25**	3	333.25**		
	2	359.75*	2	557.00*		
sni	0	9.14*	0	20.42*		
	4	97.42**	4	355.42**		
	1	227.75**	3	429.75**		
	3	240.87**	2	543.37*		
	2	298.00*	1	626.75*		
grm	4	0.42*	4	1.14*		
	3	3.25**	3	7.00*		
	0	8.14**	2	41.15**		
	2	10.87**	0	79.71**		
	1	14.75*	1	104.62*		
rr	0	2.28*	0	11.85*		
	4	51.71*	4	157.42**		
	3	95.25**	1	581.87**		
	1	99.75**	3	691.25*		
	2	198.62*	2	712.12*		
scr	4	0.85*	4	2.85*		
	3	1.12*	3	3.00*		
	2	4.12**	2	12.12**		
	0	4.71**	1	22.50**		
	1	7.50*	0	45.85*		
lck			0	0.00*		
			1	0.00*		
			2	0.00*		
			3	60.50*		
			4	490.00*		

Asterisks indicate the possible homogeneous groups—one for each column of asterisks. std, standing; mov, moving; sni, sniffing; grm, grooming; rr, rearing; scr, scratching; lck, licking. Dose: 0, vehicle; 1, 0.5 mg/kg; 2, 1,5 mg/kg; 3, 3mg/kg; 6 mg/kg.

bodies in the striatum did not abolish the *d*-AMPH-induced stereotypy because destruction of this structure made with 6-OHDA in the whole striatum attenuated or completely blocked it (21, 30). On the other hand, the striatum shows a dorsal/ventral dichotomy in function (14,32,38,39), and it has been proposed that ventral striatal aspects seem to be more necessary for the expression of stereotypy (21,39). It is suggested that *d*-AMPH has two separate actions: the release of DA from terminals in the ventral striatum (causing stereotyped behavior) and from terminals in the nucleus accumbens (causing locomotor activity), as well as the activation of a strionigral feedback loop via the dorsal striatum, leading to an inhibition in cells in the substantia nigra pars compacta (1,34,50). It is suggested that this negative feedback action of *d*-AMPH is blocked by striatal lesions, so increased DA will be released by *d*-AMPH and the production of stereotypy and locomotor activity will be enhanced (34). Inspection of the histology figures of these lesions, however, shows that kainic acid lesions spared the anteromedial aspect of the dorsal striatum, which is not true after ibotenic acid lesions (31). Probably for this reason we did not see any marked increase in locomotor and stereotyped behavior in *d*-AMPH-treated rats with ibotenic acid lesions into the dorsal striatum, a fact indicating that the anteromedial aspect of the dorsal striatum may play a major role in locomotor and stereotyped activity.

Further evidence that the dorsal striatum may not play an

important role in the expression of stereotypy after *d*-AMPH is that direct drug injection in this striatal aspect had no observable effects on behavior (5,30), while injections into the ventral striatal aspects resulted in an enhanced stereotyped biting (25).

As shown from our results, lesion of the dorsal striatum influenced more prominently some other components participating in the behavioral repertoire of *d*-AMPH, which are not in a direct relationship with the locomotor activity or stereotyped behavior. This fact indicates that the role of the dorsal striatum in behavior is more complex, a statement that has already been suggested by some authors (13).

An interesting finding was that lesioned rats did not exhibit freezing behavior. This element is a major component of the behavioral profile of *d*-AMPH but not of APO. The rat behavior is suddenly interrupted by freezing, which is exhibited at low or moderate doses of *d*-AMPH, reflecting an expression of fear and anxiety (19). A behavioral component related to freezing is "standing still," measured in a detailed study by Carr and White (5) and found to be increased after intraamygdala amphetamine infusions. Because electrical stimulation of the amygdala evokes "freezing" behavior (24), it is reasonable to conclude that the *standing still* and *freezing* responses of the two above studies represent the same behavioral element and the amygdala is primarily involved in its expression. This seems to be in agreement with our findings because the amygdala projects to the medial aspects of the dorsal striatum (37), which was damaged by ibotenic acid lesions.

Another behavioral element influenced by lesion is rearing. Rearing, a major component of the behavioral profile of *d*-AMPH, was increased in lesioned rats. It is of interest to note that infusions of *d*-AMPH into the nucleus accumbens enhanced rearing (5,25). According to our own findings, the loss of the dorsal striatum with its medial aspects led to an increase of rearing after *d*-AMPH treatment, probably indicating a relationship between NAS and rearing and an inhibitory role of the dorsal striatum on this behavioral component.

The analysis with lesion as factor did not reveal any significant difference in locomotor activity based upon photocell interruptions. It may be suggested that the lesion did not induce marked changes in locomotor activity (measured by photocell interruptions) after both drugs (*d*-AMPH and APO).

As after *d*-AMPH, lesioned rats were standing less than sham-operated rats after APO, indicating an increased behavioral activation. Lesioned rats were moving and sniffing more than sham-operated rats at the lower dose, an effect that provides some new insights into the behavioral profile of APO at low doses [decreased motor activity and yawning via the

TABLE 2B

SCHEFFE'S MULTIPLE-RANGE TESTS ($p < 0.5$) ON GROUP AVERAGES FOLLOWING ANOVA WITH DOSE AS FACTOR ON FREQUENCY, DURATION, AND MEAN DURATION OF BEHAVIORAL ELEMENTS IN APO-TREATED LESIONED RATS

	Frequency		Duration		Mean Duration	
std	4	16.37*	3	161.75*	3	9.92*
	3	17.25*	4	308.62*	4	18.04*
	2	35.87**	2	677.75**	1	19.15*
	0	38.85**	1	912.87*	2	20.09*
	1	82.75*	0	1607.00*	0	55.04*
mov	0	11.71*	0	25.00*		
	1	57.37**	1	100.50**		
	4	75.75**	4	160.25**		
	2	82.12**	2	174.75**		
	3	163.75*	3	371.75*		
sni	0	9.14*	0	20.42*		
	4	104.87**	1	383.50**		
	1	112.87**	2	496.37**		
	2	123.12**	4	511.50**		
	3	183.37*	3	852.25*		
yaw	0	0.00*	0	0.00*		
	3	0.00*	3	0.00*		
	4	1.37*	4	2.62*		
	2	1.50*	2	2.62*		
	1	7.00*	1	13.75*		
lck			0	0.00*		
			1	9.25*		
			2	34.87**		
			3	122.50**		
			4	264.25*		

Asterisks indicate the possible homogeneous groups—one for each column of asterisks. std, standing; mov, moving; sni, sniffing; yaw, yawning; lck, licking. Dose: 0, vehicle; 1, 0.25 mg/kg; 2, 0,5 mg/kg; 3, 1 mg/kg; 4, 2 mg/kg.

TABLE 3

SUMMARY OF THE EFFECTS OF IP INJECTIONS OF FOUR DOSES OF *d*-AMPH AND APO AND SALINE ON PHOTOBEAM INTERRUPTIONS AND BEHAVIORAL ELEMENTS IN LESIONED AND SHAM-OPERATED RATS

	Saline	*d*-AMPH (mg/kg, IP)				APO (mg/kg, IP)			
		0.5	1.5	3.0	6.0	0.25	0.5	1.0	2.0
pht				↓	–				
std	↓ ↑	↓ ↓	↓ ↓	↓ ↓		↓ ↓	↓	↓ ↓	
mov		↑				↑ ↑			
sni	↓↓				↑	↑ ↑		↑	
grm					–				↑
rr	↓		↑ ↑				↑		
scr	–	↑			–	↑ ↑	↑ ↑ ↑	↑ ↑	↑
frz	–	↓ ↓ –	↓ ↓ –	–	– – –	–	–	–	–
yaw		– – –	– – –	– – –	– – –				
sna	– – –		–	–	– – –				
hsw	– – –	– – –	– – –	– – –		– – –	– – –	– – –	– – –
lck	– – –	– – –	– – –	–		– – –	–		
gnw	– – –	– – –	– – –	– – –	– – –	– – –	– – –	–	–

At each element × dose intersection, the size and direction of the arrow indicate the effect of the drug injection on the corresponding element in lesioned vs. sham-operated rats. The direction of the left arrow indicates whether *d*-AMPH, APO, or saline increased or decreased the frequency of the occurrence of the corresponding behavioral element in lesioned rats' relative to sham-operated rats' respective injections. The centrally placed arrow indicates the respective differences in the duration and the right arrow in the mean duration of the behavioral elements. The two arrow lengths indicate the statistical significance of the difference (the big arrow representing a difference at the 1% level and the small arrow at the 5% level. Student's *t*-test). Only effects that were statistically significant are included here. (–), analysis was not performed. Abbreviations as in previous tables.

stimulation of presynaptic dopaminergic receptors as already suggested (7)]. This finding indicates that the dorsal striatum may play a role in the hypoactivity induced by low doses of APO.

Concerning the effects of APO, it seems that there is some doubt about the role of the striatum in the induction of stereotyped behavior. It is well established that 6-OHDA lesions of the striatum induced a supersensitivity to APO revealed by enhanced stereotyped behavior (30). On the other hand, some authors found that striatal lesions were ineffective in abolishing APO stereotypy (8,12,36). Our results are in agreement with Mason et al. (35), who did not find decrease of motor or stereotyped activation after APO in lesioned rats. On the contrary, we found a potentiation in stereotypy, which, however, did not reach any statistically significant criterion. Our results showed that the dorsal striatum influences the behavioral profile of APO in a more complex way than has been implicated until now.

The lesion of the dorsal striatum induced a marked decrease in standing behavior but did not lead to a concomitant increase in locomotor or stereotyped behaviors. The detailed behavioral recording showed that striatal lesion influenced many of the measurements of the behavioral elements, indicating that it does not play a role in the production of these behaviors but has a significant involvement in their expression. The dorsal striatum mediates behaviors originating in other brain sites (e.g. rearing–nucleus accumbens, freezing–amygdala, stereotypy–ventral striatum), possibly through heavy connections with these areas. It seems, therefore, that the dorsal striatum is involved in the expression of the behavioral activation, integrating and directing the sequential structuring of behavior.

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