Effects of Methamphetamine, Dopamine and Noradrenaline Administered into the Nucleus Accumbens of Rats Discriminating Subcutaneous Methamphetamine

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Received July 20, 1993 Accepted October 21, 1993

ABSTRACT—Since the nucleus accumbens has been hypothesized to centrally mediate the discriminative effects of psychomotor stimulants, the discriminative effects of methamphetamine (MA) as well as dopamine (DA) and noradrenaline (NA) were observed by intracerebral administration of these drugs into the nucleus accumbens in rats discriminating subcutaneous MA from saline. These rats were trained and maintained to discriminate between MA at 0.5 mg/kg, s.c. and saline under a fixed ratio 10 schedule for food reinforcement in a 2-lever operant chamber situation. Guide cannulae were implanted bilaterally into the nucleus accumbens. In the substitution tests, the drug was administered into the nucleus accumbens. MA at 10 µg per rat substituted for subcutaneous MA in 4 out of 5 rats but neither DA at 10–40 µg per rat (n=7) nor NA at 10–40 µg per rat (n=4) substituted for subcutaneous MA. On the other hand, the same drugs administered into the nucleus accumbens induced increased spontaneous motor activity as also observed in six other untrained rats. MA, DA or NA alone each at 10 µg per rat increased spontaneous motor activity. MA, DA or NA alone each at 10 µg per rat increased spontaneous motor activity. The discriminative effects of MA are considered to be mediated in the nucleus accumbens of rats. Although DA or NA alone administered into the nucleus accumbens showed similar increasing motor activity effects as those of MA, the discriminative effects of exogenous DA or NA alone administered into the same brain area were different from those of MA in the present experimental condition.

Keywords: Drug discrimination, Nucleus accumbens, Methamphetamine, Dopamine, Noradrenaline

Studies on the reinforcing and discriminative effects of drugs in animals provide useful information regarding the abuse liability of drugs. Recent studies have shown the involvement of the mesolimbic and mesocortical dopamine (DA) system in the reinforcing and discriminative effects of psychomotor stimulants (1–3). For example, rats self-administered d-amphetamine directly into the nucleus accumbens in the mesolimbic pathway (4) and cocaine into the medial prefrontal cortex in the mesocortical pathway (5). Intravenous self-administration of d-amphetamine (6) and cocaine (7–9) was disrupted by blocking DA neurons or depleting DA in the nucleus accumbens of rats. In drug discrimination studies, d-amphetamine (10) and cocaine (11) administered into the nucleus accumbens of rats substituted for these drugs administered systemically. On the other hand, neither d-amphetamine administered into other areas such as the striatum (10) nor cocaine administered into the medial prefrontal cortex or the striatum (11) substituted for these drugs administered systemically. Thus, the mediation in the nucleus accumbens of the discriminative effects of psychomotor stimulants is indicated. It was also reported from the studies using the in vivo microdialysis technique that d-amphetamine increased the synaptic concentration of DA in the nucleus accumbens of rats (12, 13). Furthermore, the DA increase caused by d-amphetamine in this brain area was positively correlated with increased locomotor activity in rats (12, 13). Thus, certain behavioral effects of amphetamines are considered to be related to dopamine release in the nucleus accumbens.

As methamphetamine (MA) is one of the most abused drugs in Japan, a series of studies covering its behavioral pharmacological effects in relation to its abuse liability have been performed at this laboratory. The purpose of the present study was to investigate the role of the nucleus accumbens in the discriminative effects of MA. MA was directly administered into this brain area of rats discriminating subcutaneous MA from saline. The substitutabili-
ity of DA and noradrenaline (NA) administered into the same brain area for the subcutaneous MA was also tested in the same rats. In order to have a general idea of the test doses of the above drugs in the drug discrimination experiment, the effects of MA, DA and NA administered into the nucleus accumbens on spontaneous motor activity were tested by using other rats in the first experiment.

MATERIALS AND METHODS

Subjects

Male Sprague-Dawley rats (jcl-SD; Clea Japan, Inc., Tokyo) were used. They were housed in individual home cages in an animal room at a controlled temperature (22±2°C) with a light/dark cycle of 12/12 hours (light on at 8:00 a.m.). In experiment 1, six untrained rats were used for spontaneous motor activity measurements. They received a free amount of food (CE-2, Clea Japan, Inc.) in their home cages, and the body weights of the rats ranged between 590 and 738 g during the drug tests. The rats used for drug discrimination training and substitution tests in experiment 2 received 15 g of food (CE-2, Clea Japan, Inc.) per rat per day in their home cages. These rats had been trained and maintained for the discrimination between MA at 0.5 mg/kg, s.c. and physiological saline at 1 ml/kg, s.c. They had previously been used for substitution tests on an antitussive mixture (14). Seven rats were used for the substitution tests in the present experiment, and their body weights ranged between 378 and 470 g during the substitution tests. All rats used in both experiments had free access to water in their home cages.

Apparatus

In experiment 1, activity cages placed on an Automex (Columbus Instruments Co., Columbus, OH, USA) were used. In experiment 2, operant chambers were used. On one wall of each chamber, two response levers were equipped. Between these levers, a light was mounted centrally above a food cup. A food pellet (50-mg pellet, Clea Japan, Inc.) was delivered by a pellet dispenser (Model G 5100; Ralph Gerbrands Co., Arlington, MA, USA). Each operant chamber as well as each activity cage was housed in a sound attenuating box with fan ventilation. Activity-count recording, lever-press response recording, and scheduling of reinforcement contingencies were performed by an LSI-11 microcomputer (Digital Equipment Co., Maynard, MA, USA) using software developed in this laboratory.

Cannulation and microinfusion

Rats were cannulated bilaterally into the nucleus accumbens. Bilateral guide cannulae assemblies were made from 26-gauge stainless steel hypodermic tubing. Cannulae were implanted under sodium pentobarbital (Nembutal 40 mg/kg, i.v.) anesthesia using coordinates from Paxinos and Watson (15). Coordinates for cannulation were 1.7-mm anterior, 1.4-mm lateral, and 6.1-mm ventral from the bregma. Drug solution was infused by the microinfusion technique performed by using a 33-gauge cannula inserted inside the guide cannulae. The infusion cannula was attached to 22-gauge polyethylene tubing using acrylic glue. The infusion cannula was cut 1 mm longer than the guide cannulae. Once the cannula was inserted, the infusion was made by hand using a volume of 0.4 μl per side (0.8 μl per rat) over a 30-sec period. For this infusion, 22-gauge tubing was connected to a 5-μl Hamilton syringe. At the end of the experiments, rats were sacrificed with an overdose of Nembutal. Cannulae placement was verified histologically. Only the behavioral data of rats with accurate placement of cannulae were used for the analysis.

Drugs

Methamphetamine hydrochloride (Dainippon Pharmaceutical Co., Osaka), dopamine hydrochloride (3-hydroxytyramine, Sigma Chemical Co., St. Louis, MO, USA), and noradrenaline ((−)arterenol, Sigma Chemical Co.) were obtained commercially. MA was dissolved in physiological saline, and DA and NA were dissolved in distilled water. The concentrations of MA, DA and NA for microinfusion into the nucleus accumbens in experiments 1 and 2 were adjusted so that the final infusion volume was 0.4 μl. The concentration of subcutaneously administered MA for drug discrimination training in experiment 2 was 0.5 mg/ml. Drug dosages were given in terms of the salt.

Experiment 1. Spontaneous motor activity measurements

Rats implanted with bilateral guide cannulae into the nucleus accumbens were repeatedly used for drug tests. In the activity count measurements, each rat was placed into an activity cage between 2 p.m. and 4 p.m. and habituated for 2 hr. Then the rats were removed from the activity cages, and either a vehicle (distilled water), MA, DA or NA at a certain dose was administered into the nucleus accumbens. Just after the administration, the rats were placed again into the activity cages, and their activity counts were recorded every 10 min for 40 min. In this experiment, each of the administration tests with MA, DA and NA at a certain dose was administered into the nucleus accumbens. Just after the administration, the rats were placed again into the activity cages, and their activity counts were recorded every 10 min for 40 min. In this experiment, each of the administration tests with MA, DA and NA with 10 and 20 μg per rat was performed with an interval of at least 1 week.

Experiment 2. Methamphetamine discrimination and substitution tests

Discrimination training: Details of the discrimination
and the fact that every tenth consecutive response on sessions except for the duration of the test session (2 min) was identical with that during the discrimination training administration. During the 2-min test session, the procedure was performed 10-min after each administration with an interval of 13 min. Each of the 2 rats (total administered dose, 40 µg per rat) were repeated dose, 20 µg per rat), and finally the test drug at 20 µg per rat) was administered, then a test drug at an initial dose determined by repeated administration of the same drug in a cumulative dose procedures (14, 16). In this procedure, the dose-effect relationship of each test drug was determined in the same manner as above. Then the substitutability of the discriminative effects of MA, DA or NA administered into the nucleus accumbens was tested. In each substitution test, 2 or 3 doses of each drug was tested in a single day by using a procedure modeled after cumulative dose procedures (14, 16). In this procedure, the dose-effect relationship of each test drug was determined by repeated administration of the same drug in a single day. First, a vehicle (saline for MA test, or distilled water for DA and NA tests) at 0.4 µl per side (0.8 µl per rat) was administered, then a test drug at an initial dose (10 µg per rat), the same drug at 10 µg (total administered dose, 20 µg per rat), and finally the test drug at 20 µg per rat (total administered dose, 40 µg per rat) were repeatedly administered with an interval of 13 min. Each of the 2-min test sessions was performed 10-min after each administration. During the 2-min test session, the procedure was identical with that during the discrimination training sessions except for the duration of the test session (2 min) and the fact that every tenth consecutive response on either lever produced food reinforcement during the session. The one-day substitution tests were interspersed with daily discrimination training sessions, and they were only performed after the discrimination criterion described above had been satisfied for at least 3 consecutive daily discrimination training sessions.

Data analysis

In experiment 1, activity counts recorded every 10 min were used for the analysis. The counts were averaged across rats for each drug dose and compared statistically by the Student's paired two-tailed t test against the vehicle control. In each substitution test in experiment 2, the percent of MA-appropriate responses out of the total responses, and the total response rate per min during each of the 2-min sessions were calculated. These figures were averaged across rats for each drug dose. No statistical test was performed in this experiment.

RESULTS

Experiment 1. Spontaneous motor activity measurements

Effects of MA, DA and NA administered into the nucleus accumbens on spontaneous motor activity are presented in Table 1. In each drug test, 6 rats were used; however, one rat was excluded during the experiment due to technical problems with the guide cannulae.

After administration of distilled water at 0.8 µl per rat into the nucleus accumbens, the mean of spontaneous motor activity counts across 6 rats was 201.0 during the 0–10-min period, and the means of the counts decreased time-dependently.

After administration of MA at 10 µg per rat into the nucleus accumbens, the counts increased significantly during any 10-min period compared to the comparable periods of the vehicle control. At 20 µg per rat, the counts during the 30–40-min period increased significantly, and the counts during the other 10-min periods tended to increase compared to the comparable periods of the vehicle control. After administration of DA at 10 µg per rat into the nucleus accumbens, the counts during the 0–10-min period increased significantly and the counts during the other periods tended to increase. At 20 µg per rat, the counts during the 30–40-min period increased significantly, and the counts during the other periods tended to increase. After administration of NA at 10 µg per rat into the nucleus accumbens, the counts during any 10-min period increased significantly. However, no significant increase was observed with NA at 20 µg per rat during any period.
Table 1. Effects of methamphetamine, dopamine and noradrenaline administered into the nucleus accumbens on spontaneous motor activity in rats

| Drug             | Dose (μg/rat) | 0–10 min        | 10–20 min        | 20–30 min        | 30–40 min        |
|------------------|---------------|-----------------|-----------------|-----------------|-----------------|
| Distilled water  | 0.8 μl/rat    | 201.0 ± 48.7    | 93.7 ± 40.8     | 34.5 ± 14.7     | 16.5 ± 7.7      |
| Methamphetamine | 10            | 557.0 ± 87.5**  | 584.0 ± 107.8** | 566.0 ± 122.5** | 426.2 ± 113.4*  |
| Methamphetamine | 20*           | 264.4 ± 69.8    | 276.6 ± 119.1   | 263.2 ± 132.6   | 191.6 ± 58.3*   |
| Dopamine         | 10            | 310.8 ± 61.1*   | 240.2 ± 80.5    | 197.3 ± 103.3   | 69.8 ± 54.8     |
| Dopamine         | 20            | 248.3 ± 61.7    | 197.8 ± 44.3    | 131.2 ± 43.7    | 124.2 ± 48.1*   |
| Noradrenaline    | 10            | 313.3 ± 58.8**  | 257.7 ± 69.6*   | 175.0 ± 47.0*   | 156.2 ± 47.0*   |
| Noradrenaline    | 20*           | 150.0 ± 48.5    | 102.6 ± 33.6    | 90.3 ± 30.0     | 89.6 ± 40.6     |

* The means of activity counts with standard errors during each 10-min period after administration. N=5, otherwise N=6. *: P < 0.05, **: P < 0.01 against the vehicle (distilled water) control.

Experiment 2. Methamphetamine discrimination and substitution tests

Substitution test results with MA, DA and NA administered into the nucleus accumbens are presented in Table 2. Seven rats were used initially; however, three rats were finally excluded during the experiment due to technical problems with the guide cannulae.

With vehicles (saline or distilled water) in the first 2-min test session in each of the substitution tests with MA, DA and NA, the mean percent of MA-appropriate responses out of the total responses ranged between 0.0 and 0.3%, and the mean total response rate per min ranged between 37.5 and 60.8.

In the substitution test with MA, the mean percent of MA-appropriate responses was 78.7% and 4 out of 5 rats showed 80% or more MA-appropriate responses at 10 μg per rat. At the total administered dose of 20 μg per rat, the mean percent of MA-appropriate responses decreased to 41.8%, and only 2 out of 5 rats showed 80% or more MA-appropriate responses. The mean total response rate per min did not decrease with MA dose-dependently. In the substitution test with DA, the mean percent of MA-appropriate responses ranged between 2.9 and 12.6% at 10–40 μg per rat, and only one out of 7 rats showed 80% or more MA-appropriate responses at 10 μg per rat. The mean total response rate per min did not change markedly across the doses tested. In the substitution test with NA, the mean percent of MA-appropriate responses ranged between 0.0 and 2.0% at 10–40 μg per rat, and none of the rats showed 80% or more MA-appropriate responses. The mean total response rate per min decreased with NA dose-dependently.

Table 2. Substitution tests with methamphetamine, dopamine and noradrenaline administered into the nucleus accumbens of rats discriminating methamphetamine at 0.5 mg/kg, s.c. from saline

| Drug             | Total administered dose (μg/rat) | MA-appropriate responses (%) | Response rate per min | n/N*               |
|------------------|---------------------------------|------------------------------|-----------------------|--------------------|
| Saline           | 0.8 μl/rat                      | 0.3 ± 0.3                    | 37.5 ± 7.6            | 0/5                |
| Methamphetamine | 10                              | 78.7 ± 19.7                  | 46.2 ± 3.8            | 4/5                |
| Methamphetamine | 20                              | 41.8 ± 23.8                  | 56.4 ± 9.4            | 2/5                |
| Distilled water  | 0.8 μl/rat                      | 0.2 ± 0.2                    | 50.3 ± 7.7            | 0/7                |
| Dopamine         | 10                              | 12.6 ± 12.6                  | 59.6 ± 9.8            | 1/7                |
| Dopamine         | 20                              | 11.1 ± 11.1                  | 53.0 ± 8.4            | 0/7                |
| Dopamine         | 40                              | 2.9 ± 1.9                    | 44.1 ± 12.1           | 0/7                |
| Distilled water  | 0.8 μl/rat                      | 0.0 ± 0.0                    | 60.8 ± 8.7            | 0/4                |
| Noradrenaline    | 10                              | 0.3 ± 0.3                    | 55.0 ± 13.6           | 0/4                |
| Noradrenaline    | 20                              | 0.0 ± 0.0                    | 38.9 ± 19.5           | 0/4                |
| Noradrenaline    | 40                              | 2.0 ± 1.2                    | 19.5 ± 14.8           | 0/4                |

* The means and standard errors of the total MA (methamphetamine)-appropriate responses and the total response rate per min during each 2-min session. n/N indicates the number of rats showing 80% or more MA-appropriate responses (n) out of the total number of rats tested (N).
DISCUSSION

In the present study, discrimination between MA at 0.5 mg/kg, s.c. and saline was established in rats. The dose of MA for discrimination training was selected based on data obtained from a schedule-controlled behavior experiment in rats performed at our laboratory where MA at 0.5 mg/kg, s.c. clearly increased the response rate. Within 37 sessions, the rats used for the present study attained the training criterion for the establishment of discrimination between MA at 0.5 mg/kg, s.c. and saline as described elsewhere (14). In the substitution tests, a repeated dose procedure consisting of each 2-min session was used to obtain data efficiently before the occurrence of technical problems with the guide cannulae. It was reported in our previous study that the repeated subcutaneous administration of MA under the same procedure as in the present study produced MA-appropriate responses dose-dependently, and the complete substitution for MA at the single training dose (0.5 mg/kg, s.c.) was observed (14). It was also reported in the same study that the repeated subcutaneous administration of saline consistently produced saline-appropriate responses. These results may indicate that the present repeated dose procedure is appropriate for observing discriminative effects of test drugs in terms of substitution for subcutaneous MA. Although the comparison between the dose-effect function under the repeated dose procedure and that under the single dose procedure was not performed in the present study, studies using a repeated (cumulative) dosing procedure demonstrated good correlations of the results between a single dose procedure and a cumulative one (16).

In the present experiment, the first dose of MA, DA and NA for the substitution tests was set at 10 μg per rat because each drug at this dose produced behavioral effects, as shown by an increase of spontaneous motor activity in experiment 1.

The mean MA-appropriate responses after MA at 10 μg per rat administered into the nucleus accumbens was 78.7%, a value was very close to the training criterion of 80%, and the substitution at this dose for subcutaneous MA was observed in 4 out of 5 rats. These results are in agreement with other results that indicated mediation in the nucleus accumbens of the discriminative effects of d-amphetamine and cocaine (10, 11). The doses of d-amphetamine and cocaine administered into the nucleus accumbens in the substitution for each drug administered systemically were, respectively, 5 μg and 20 μg per rat in the above studies. The dose of MA in the present substitution was inbetween the above doses. Thus, the present results may give further evidence that the discriminative effects of psychomotor stimulants are mediated in the nucleus accumbens.

It is considered that behavioral effects of psychomotor stimulants such as amphetamines and cocaine are mainly produced by the release of DA from the dopaminergic neurons as well as the release and the reuptake block of NA from the noradrenergic neurons (17). Thus, the substitutability of the exogenous DA or NA alone administered into the nucleus accumbens for subcutaneous MA was also tested. However, neither exogenous DA nor NA administered into this brain area substituted for subcutaneous MA. The reason for this lack of the substitution of DA or NA alone is not certain. However, it is considered that the repeated administration of exogenous DA or NA may cause acute tolerance or that the manners and rates of distribution and transformation of these drugs may be different from those of endogenous DA or NA released by amphetamines. There is a possibility that both DA and NA must be administered together to mimic the discriminative effects of MA. As it is also possible that serotonin is involved, it is likely that MA increases the release of all these transmitters within the nucleus accumbens. Administration of either compound alone may be insufficient to mimic the same discriminative effects as those of MA. Different doses of DA and NA at various time intervals should have also been tested.

MA, DA or NA alone administered into the nucleus accumbens increased spontaneous motor activity in the present experiment. This may indicate that the effects of MA, DA or NA in increasing spontaneous motor activity are at least partly mediated in the nucleus accumbens. The fact that amphetamine, DA or NA alone administered into the nucleus accumbens increased motor activities of rats was also reported by other investigators (13, 18). However, the activity increase by NA administered into the nucleus accumbens was only found when it was pretreated with nialamide, a monoamine oxidase inhibitor (MAOI); and a decrease rather than increase was found by NA without the MAOI pretreatment (19). The reason for the disagreement in the above results and the present results that demonstrated an increase of spontaneous motor activity by NA without any MAOI pretreatment is not certain.

The similar or dissimilar behavioral pharmacological effects of MA to the effects of exogenous DA or NA were manifested differently depending on the type of behavioral pharmacological effects one observed. The manners of mediation in the nucleus accumbens in producing certain behavioral effects are probably different among the drugs.

In conclusion, the discriminative effects of MA are considered to be mediated in the nucleus accumbens in rats. Although DA or NA alone administered into the nucleus accumbens showed similar increasing motor activity effects as those of MA, the discriminative effects of ex-
ogenous DA or NA alone administered into the same brain area were different from those of MA in the present experimental condition.

Acknowledgments

This research was supported by a grant for studies in Neuropsychiatric Diseases covering research into drug dependence (1987–1989) from the Ministry of Health and Welfare of Japan.

REFERENCES

1. Nielsen, E.B., Randrup, K. and Andersen, P.H.: Amphetamine discrimination: effects of dopamine receptor agonists. Eur. J. Pharmacol. 160, 253–262 (1989)
2. Woolverton, W.L.: Effects of a D1 and D2 dopamine antagonist on the self-administration of cocaine and piribedil by rhesus monkeys. Pharmacol. Biochem. Behav. 24, 531–535 (1986)
3. Woolverton, W.L., Goldberg, L.I. and Ginos, J.Z.: Intravenous self-administration of dopamine receptor agonists by rhesus monkeys. J. Pharmacol. Exp. Ther. 230, 678–683 (1984)
4. Hoebel, B.G., Monaco, A.P., Hernandez, L., Aulisi, E.F., Stunley, B.G. and Lenard, L.: Self-injection of amphetamine directly into the brain. Psychopharmacology (Berlin) 81, 158–163 (1983)
5. Goeders, N.E. and Smith, J.E.: Cortical dopaminergic involvement in cocaine reinforcement. Science 221, 773–775 (1983)
6. Lyness, W.H., Friedle, N.M. and Moore, K.E.: Destruction of dopaminergic nerve terminals in nucleus accumbens: Effect on d-amphetamine self-administration. Pharmacol. Biochem. Behav. 11, 555–556 (1979)
7. Roberts, D.C.S., Cocoran, M.E. and Fibiger, H.C.: On the role of ascending catecholaminergic systems in intravenous self-administration of cocaine. Pharmacol. Biochem. Behav. 6, 615–620 (1977)
8. Roberts, D.C.S., Koob, G.F., Klonoff, P. and Fibiger, H.C.: Extinction and recovery of cocaine self-administration following 6-hydroxydopamine lesions of the nucleus accumbens. Pharmacol. Biochem. Behav. 12, 781–787 (1980)
9. Roberts, D.C.S. and Zito, K.A.: Interpretation of lesion effects on stimulant self-administration. In Methods of Assessing the Reinforcing Properties of Abused Drugs, Edited by Bozarth, M.A., pp. 87–103, Springer-Verlag, New York (1987)
10. Nielsen, E.B. and Scheel-Kruger, J.: Cueing effects of amphetamine and LSD: Elicitation by direct microinjection of the drugs into the nucleus accumbens. Eur. J. Pharmacol. 125, 85–92 (1986)
11. Wood, D.M. and Emmet-Oglesby, M.W.: Mediation in the nucleus accumbens of the discriminative stimulus produced by cocaine. Pharmacol. Biochem. Behav. 33, 453–457 (1989)
12. Hernandez, L., Lee, F. and Hoebel, B.G.: Simultaneous microdialysis and amphetamine infusion in the nucleus accumbens and striatum of freely moving rats: Increase in extracellular dopamine and serotonin. Brain Res. Bull. 19, 623–628 (1987)
13. Sharp, T., Zetterstrom, T., Ljungberg, T. and Ungerstedt, U.: A direct comparison of amphetamine-induced behaviours and regional brain dopamine release in the rat using intracerebral dialysis. Brain Res. 401, 322–330 (1987)
14. Ando, K. and Yanagita, T.: Effects of an antitussive mixture and its constituents in rats discriminating methamphetamine from saline. Pharmacol. Biochem. Behav. 41, 783–788 (1992)
15. Paxinos, G. and Watson, C.: The Rat Brain in Stereotaxic Coordinates, 2nd edition, Academic Press, San Diego (1986)
16. Wenger, G.R.: Cumulative dose-response curves in behavioral pharmacology. Pharmacol. Biochem. Behav. 13, 647–651 (1980)
17. Moore, K.E.: Amphetamines: Biochemical and behavioral actions in animals. In Handbook of Psychopharmacology, Vol. II, Stimulants, Edited by Iversen, L.L., Iversen, S.D. and Snyder, S.H., pp. 41–98, Plenum Press, New York (1978)
18. Pijnenburg, A.J.J., Honig, W.M.M. and Van Rossum, J.M.: Effects of antagonists upon locomotor stimulation induced by injection of dopamine and noradrenaline into the nucleus accumbens of nialamide-pretreated rats. Psychopharmacologia (Berlin) 41, 175–180 (1975)
19. Pijnenburg, A.J.J., Honig, W.M.M., Van Der Heyden, J.A.M. and Van Rossum, J.M.: Effects of chemical stimulation of the mesolimbic dopamine system upon locomotor activity. Eur. J. Pharmacol. 35, 45–58 (1976)