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Suppression of Exploratory Locomotor Activity by the Local Application of Dopamine or *l*-Noradrenaline to the Nucleus Accumbens of the Rat

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SVENSSON, L. AND S. AHLENIUS. *Suppression of exploratory locomotor activity by the local application of dopamine or l-noradrenaline to the nucleus accumbens of the rat.* PHARMACOL BIOCHEM BEHAV **19**(4) 693–699, 1983.—Adult male Sprague-Dawley rats were administered dopamine (DA) or *l*-noradrenaline (*l*-NA) locally into the nucleus accumbens or in the neostriatum. Six minutes following the injections the animals were placed in an open field arena (700×700 mm) and their locomotor activity was recorded every 3 min for maximally 60 min. In the nucleus accumbens both DA (10–160 μg/side) and *l*-NA (2.5–40 μg/side) produced a suppression of the initial (0–3 min) exploratory locomotor activity in the open field arena. The highest doses of the respective drug, 80–160 μg of DA and 20–40 μg of *l*-NA, produced stimulation of the locomotor activity at a later time interval (6–9 min). The number of rearings during the initial exploration (0–3 min) was suppressed by DA (10–160 μg/side) as well as by *l*-NA (2.5–40 μg/side). When administered to the neostriatum, DA (80–160 μg/side) produced a stimulation of locomotor activity, 6–9 min after placement in the open field. The administration of *l*-NA (20–80 μg/side) to the neostriatum produced a suppression of the exploratory locomotor activity (0–6 min). The number of rearings were reduced by the administration of *l*-NA (20–80 μg/side) whereas no significant effect was observed after the administration of DA (5–160 μg/side). As assessed in the present experiments DA and *l*-NA produced identical effects in the nucleus accumbens, *l*-NA being about 4 times as potent as DA, whereas opposite effects were produced by *l*-NA and DA when applied to the neostriatum.

Dopamine Noradrenaline Open field Nucleus accumbens Neostriatum Rat

THE LOCAL application of dopamine (DA) into the nucleus accumbens produces hyperactivity in rats pretreated with nialamide [7,27] or nialamide and reserpine [16]. *l*-Noradrenaline (*l*-NA) is much less effective in this regard and the effects appear, at least partially, to be mediated via nucleus accumbens DA [8,26] although effects obtained in reserpine-treated animals indicate some direct effects by *l*-NA in this structure [16]. When DA is locally applied into the nucleus accumbens of normal rats there is also an increase in locomotor activity, although of shorter duration [25]. In addition, when observing the animals during the initial explorative phase in a new environment, it is possible to observe a decrease in the locomotor activity by low doses of DA [36]. Thus, the dose-response curve obtained after intra-accumbens injections of DA is similar to the curve obtained after systemic administration of *L*-DOPA or other drugs resulting in activation of central DA receptors [29] indicating a preferential action at autoreceptors at low doses and a preferential postsynaptic activation at higher doses [31].

Unexpectedly we recently found that when observed during the initial exploratory phase, *l*-NA produced effects very similar to the effects produced by DA when applied to the nucleus accumbens in normal rats. Furthermore, *l*-NA was about 4 times as potent as DA in inducing depression and stimulation of locomotor activity respectively [32,33]. We now give a full account of these experiments. In addition, we have investigated the effects of DA and *l*-NA in the neostriatum. We have followed the effects during habituation to an open field and in order to improve the analysis of drug-induced behavioral change we have recorded activity in the periphery and in the center of the arena separately and also recorded the number of rearings.

METHOD

Animals

Adult male Sprague-Dawley rats (Anticimex, Sollentuna, Sweden) were used. The animals were maintained under conditions of constant dark-light cycle (dark 11 a.m.–11 p.m.), temperature and relative humidity with food and water available at all times.

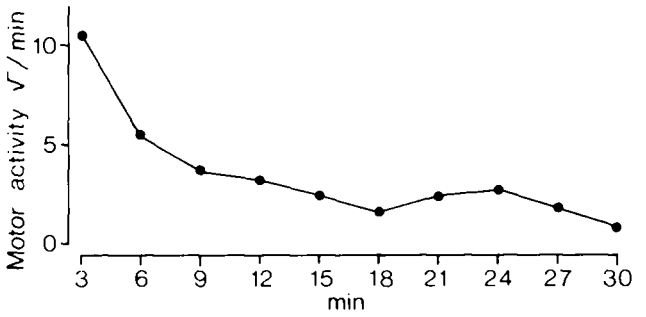

FIG. 1. Locomotor activity of the saline-treated controls used in the experiments. The animals were placed in the open field arena six minutes following completion of the saline intracerebral injections. Shown are the means of 30 animals injected into the nucleus accumbens (18) or in the neostriatum (12). The data were subjected to a two-way ANOVA. No difference was found in activity between animals injected in the nucleus accumbens or in the neostriatum: $F(1,28)=0.25$, n.s. The decrease in activity over time was statistically significant: $F(9,252)=29.16$, $p<0.001$. Individual comparisons showed that the drop in activity between the 0–3 and 3–6 min and between the 3–6 and 6–9 min intervals were statistically significant ($t=9.34$, $p<0.001$; $t=2.82$, $p<0.01$, respectively; t-test for correlated samples). No further statistically significant differences were found between successive 3 min intervals.

Drugs

Dopamine·HCl (Sigma, St. Louis, MI), *l*-noradrenaline·HCl (Fluka, Buchs, Switzerland), *d*-noradrenaline·HCl (prepared at the Department of Pharmacology, University of Göteborg by Dr. Tor Magnusson from *d*-noradrenaline bitartrate, Adams Chemical Co., Round Lake, IL). All drugs were dissolved in 0.9% saline. The doses refer to the forms indicated above.

Surgery and Intracerebral Injections

One week upon arrival from the breeder, at a weight of 260–300 g, the animals were deeply anaesthetized (Mebumal™, 60 mg/kg IP) and mounted in a stereotaxic instrument. Holes were drilled and guide cannulae (internal diameter 0.45 mm) were placed bilaterally on the skull and permanently fixed by means of acrylic dental cement. The guide cannulae were placed 1.2 mm from the midline and 2.3 mm in front of the bregma for injections into the nucleus accumbens and 2.4 mm from the midline and 1.3 mm in front of the bregma for injections into the neostriatum. The tip of the guide cannulae reached the level of the dura mater.

Twenty-four to 30 hr after the operation intracerebral injections were made through the guide cannulae by means of injection cannulae (internal diameter; 0.20–0.25 mm). The injection cannulae were lowered to a level 6.8 mm below the dura mater for injections into the nucleus accumbens and 4.4 mm below the dura mater for injections into the neostriatum. The coordinates were derived from the atlas by König and Klippel [20]. The injection cannulae were attached to Hamilton 5 μl syringes (No. 75N). The depth of penetration was controlled by means of a stopper on the injection cannulae. The injection volume was held constant at 1 μl, injected for 10 sec, and the injection cannulae were kept in place for 60 sec before being retracted. The bilateral injections were made in series with a 90 sec pause between injections. The animals did not struggle or showed other signs of discomfort during injections.

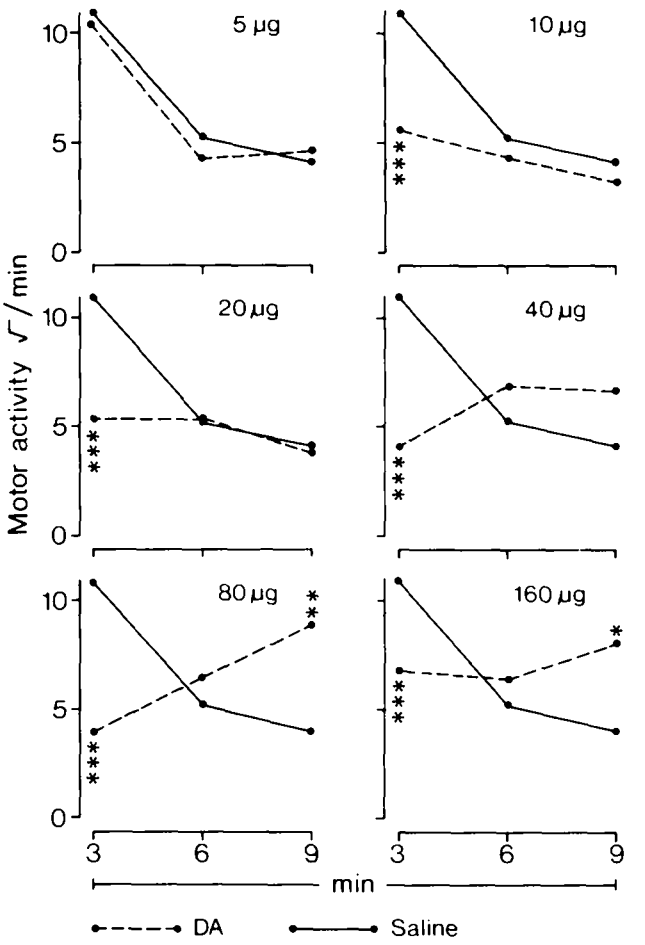

FIG. 2. Effects of bilateral application of dopamine (DA), 5–160 μg/side, into the nucleus accumbens on locomotor activity of the rat. The animals were given DA 6 min before being placed in the open field arena as described in the Method section. Shown are the means of 4–6 animals/dose of DA and the means of the same 18 saline injected controls included in each graph for comparison. The mean+S.D. of these animals at the three time intervals was 11.1±1.1, 5.2+2.9 and 4.1±3.4 respectively. Statistical comparison with saline treated controls at the respective dose and time interval: $*p<0.05$, $**p<0.01$, $***p<0.001$, all other comparisons n.s.

Open Field Observations

Six min after completion of the injection procedure, the animals were placed in a dark, square, open field arena equipped with two rows of horizontally placed infralight sensitive photocells at right angles (8 plus 8 photocells). Photocells are placed 100 mm apart except that the last cell in each row is placed 25 mm from the corner and 75 mm from the next photocell in the same row. The arena measures 700×700 mm.

Horizontal and vertical activity was recorded every 3 min for maximally 60 min by means of a digital printer (Newport, digital printer, M810), connected to a buffer memory accumulating photocell beam interruptions. In addition to the total activity counts, separate counts were obtained for the peripheral activity (within 25 mm from the wall).

Histology

After completion of the activity measurements the

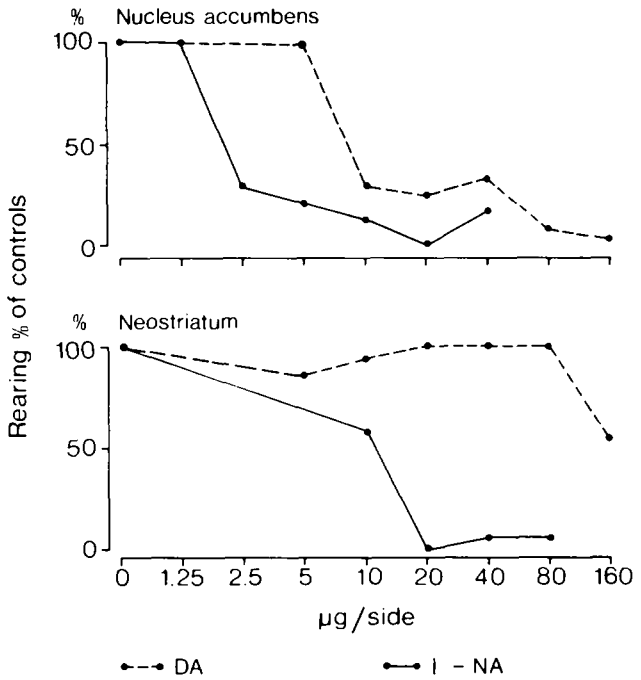

FIG. 3. Effects of bilateral application of dopamine (DA) or *l*-noradrenaline (*l*-NA) into the nucleus accumbens or the neostriatum on rearing of the rat. The animals were given DA or *l*-NA 6 min before rearing was recorded (0–3 min). Shown are the means of 4–10 animals/experimental group expressed as percent of 18 (nucleus accumbens) and 12 (neostriatum) saline injected controls (2.4±0.9 and 6.3±2.7 respectively). Statistical comparisons with saline treated controls as follows. Nucleus accumbens DA: 2.5–10 µg/side n.s., 10–160 µg/side all comparisons $p<0.001$; *l*-NA: 1.25 µg/side n.s., 2.5–80 µg/side all comparisons $p<0.001$. Neostriatum *l*-NA: 10 µg/side $p<0.05$, 20–80 µg/side all comparisons $p<0.001$.

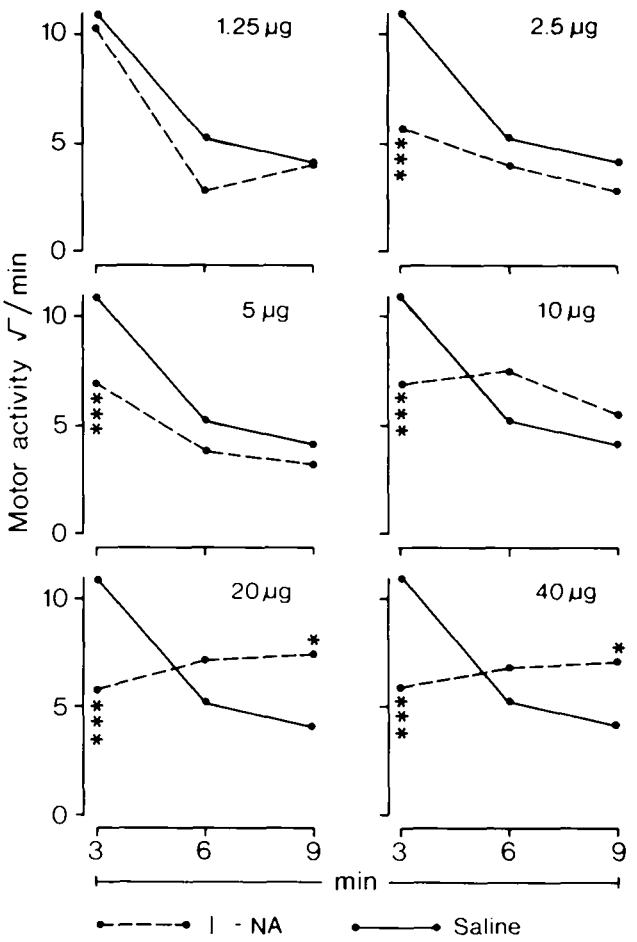

FIG. 4. Effects of bilateral application of *l*-noradrenaline (*l*-NA), 1.25–40 µg/side, into the nucleus accumbens on locomotor activity of the rat. Time of injections as in Fig. 2. Shown are the means of 5 animals/dose of *l*-NA and the same 18 saline treated controls included in each graph for comparison. Statistical comparisons with saline treated controls at the respective dose and time interval: $^{*}p<0.05$, $^{***}p<0.001$, all other comparisons n.s.

animals were decapitated and the brain was removed and stored in 10% formalin for at least 10 days. The formalin-treated brains were frozen and cut at 50 µm on a microtome. The sections were mounted on glass slides for inspection under microscope. Only those animals, in which the injection cannulae tracks could be followed to the nucleus accumbens or the neostriatum, were accepted in the analysis of the results.

Experimental Design and Statistical Analysis

In the first series of experiments 0.9% saline, different doses of DA·HCl, *l*-NA·HCl or *d*-NA·HCl were locally applied in the nucleus accumbens in different groups of animals. These experiments (Fig. 2, 4 and 5) have the same saline injected control group. At least one saline injected animal was run together with one or more drug treated animals on any given day. Similarily, in the following experiments where animals were given different doses of DA·HCl or *l*-NA·HCl in the neostriatum, a common control group was run in parallel (Fig. 6 and 7). It was found that saline treated controls habituate at a fast rate within 9 min of exposure to the open field area (Fig. 1). Thus this time interval was used in the analysis of drug-induced changes in the normal pattern of locomotion. In order to evaluate possible drug-induced effects on habituation a linear trend analysis was carried out [37]. The effects of DA·HCl, *l*-NA·HCl or *d*-NA·HCl on locomotion and rearing in the nucleus accumbens experiment, and the effects of DA·HCl or *l*-NA·HCl on the same variables in the neostriatal experiment, were evaluated separately by means of a one-way ANOVA followed by *t*-test [37]. The locomotor activity or rearing scores were subjected to a square root transformation prior to statistical evaluation. $p>0.05$ was considered as not significant (n.s.).

RESULTS

Nucleus Accumbens

Effects of dopamine (DA). Initially (0–3 min) the local bilateral application of DA into the nucleus accumbens, 10–160 µg/side, produced a statistically significant depression of the locomotor activity in comparison with saline injected controls, $F(6,44)=33.36$, $MS_{error}=2.25$, $p<0.001$ (Fig. 2). At the highest doses of DA, 80 and 160 µg/side there was a statistically significant increase in the locomotor activity at a later time interval, $F(6,44)=3.34$, $MS_{error}=9.68$, $p<0.01$ (6–9 min). There were no statistically significant changes 3–6 min, $F(6,44)=0.88$, $MS_{error}=6.76$, n.s., or in peripheral/total activity. Continued observations indicated that the duration

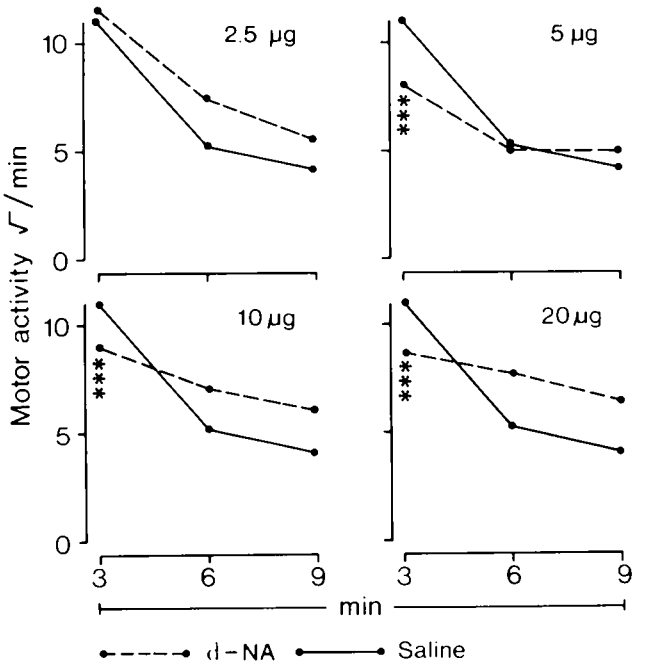

FIG. 5. Effects of bilateral application of *d*-noradrenaline (*d*-NA), 2.5–20 µg/side, into the nucleus accumbens on locomotor activity of the rat. Time of injections as in Fig. 2. Shown are the means of 5 animals/dose of *d*-NA and the same 18 saline treated controls included in each graph for comparison (cf., Fig. 2). Statistical comparisons with saline treated controls at the respective dose (0–3 min). ***$p<0.001$, all other comparisons n.s.

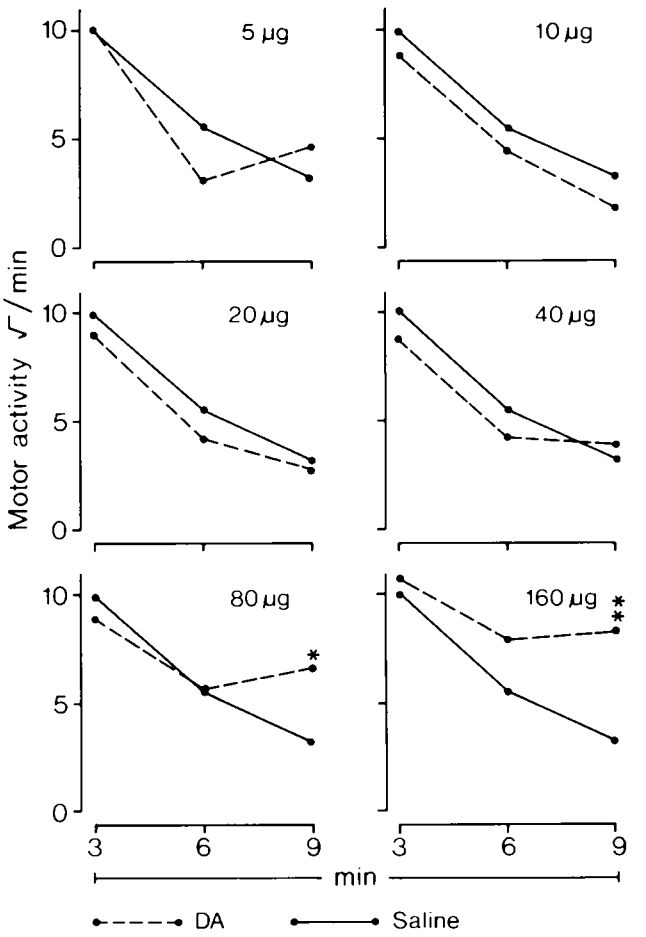

FIG. 6. Effects of bilateral application of dopamine (DA), 5–160 µg-side, into the neostriatum on locomotor activity of the rat. Time of injections as in Fig. 2. Shown are the means of 5–10 animals/dose of DA and the same 12 saline treated controls included in each graph for comparison. The mean±S.D. of these animals at the three time intervals was 10.0±1.6, 5.5±2.7 and 3.2±3.2 respectively. Statistical comparisons with saline treated controls at the respective dose (6–9 min): *$p<0.05$, **$p<0.01$, all other comparisons n.s.

of the increase in locomotion was at least 45 min. Except for the lower doses of DA, 5 and 10 µg/side, there was no indication of habituation in the DA-injected animals. The number of rearings was statistically significantly suppressed by the injection of DA, 10–160 µg/side, $F(7,47)=13.66$, $MS_{error}=0.59$, $p<0.001$ (Fig. 3). All drug-injected animals, whether sedated or stimulated, displayed normal coordinated movements. Visual inspection of some animals showed that the stimulation of locomotor activity caused by the highest doses of DA was characterized by a sterotyped forced locomotion as also indicated by a failure to habituate and a loss of rearings.

Effects of l-noradrenaline (l-NA). The local, bilateral application of *l*-NA, 2.5–40 µg/side, produced a statistically significant suppression of the locomotor activity during the first 3 min of the test in comparison with saline controls, $F(6,41)=17.13$, $MS_{error}=2.69$, $p<0.001$ (Fig. 4). At the later time interval (6–9 min) the administration of higher doses, 20 and 40 µg/side, resulted in a statistically significant stimulation of the locomotor activity, $F(6,41)=2.65$, $MS_{error}=6.92$, $p<0.05$. There were no statistically significant changes at 3–6 min, $F(6,41)=2.58$, $MS_{error}=6.60$, n.s. The duration of the stimulation was less than 30 min at both doses.

An additional group of animals was given 80 µg/side of *l*-NA and the effects were similar to those obtained by 20 and 40 µg/side: 6.4, 6.4 and 6.5 $\sqrt{\times}$ counts/min at 0–3, 3–6 and 6–9 min respectively. The duration of the stimulation induced by this dose was at least 30 min. At lower doses there appeared to be some habituation, however, there were no signs of habituation in animals given 10–80 µg/side of *l*-NA. The number of rearings was statistically significantly suppressed by *l*-NA in doses of 2.5–80 µg/side, $F(7,43)=13.42$, $MS_{error}=0.55$, $p<0.001$ (Fig. 3). There were no major changes in peripheral/total activity at any dose or time interval.

Thus, as measured under the present conditions there were no qualitative differences in the pattern of movements in animals given *l*-NA as compared to animals given DA. However, animals given the highest doses (20–80 µg/side) of *l*-NA displayed a characteristic forced respiration and occasional screams.

Effects of d-noradrenaline (d-NA). Compared to controls, there was a slight but consistent, statistically significant, suppression of the locomotor activity by the administration of *d*-NA, 5–20 µg/side, during the first 3 min of observation, $F(4,33)=13.52$, $MS_{error}=1.27$, $p<0.001$, (Fig. 5). No other statistically significant effects were obtained by the doses tested (2.5–20 µg/side), 3–6 min: $F(4,33)=1.73$, $MS_{error}=6.47$, n.s, 6–9 min: $F(4,33)=1.14$, $MS_{error}=7.31$, n.s.

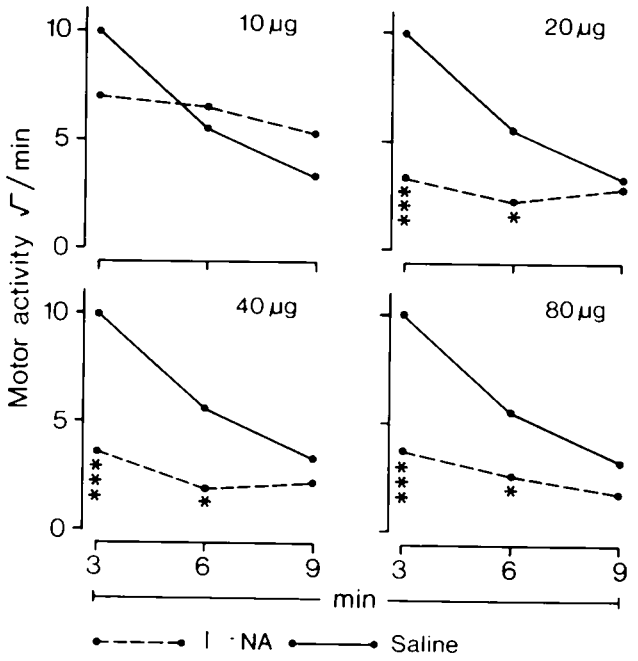

FIG. 7. Effects of bilateral application of *l*-noradrenaline (*l*-NA), 10–80 μg/side, into the neostriatum on locomotor activity of the rat. Time of injections as in Fig. 2. Shown are the means of 4–6 animals/dose of *l*-NA and the same 12 saline treated controls included in each graph for comparison (cf., Fig. 6). Statistical comparisons with slaine treated controls at the respective dose and time interval. $*p<0.05$, $***p<0.001$, all other comparisons n.s.

Neostriatum

Effects of dopamine (DA). The only effect on locomotor activity by the administration of DA bilaterally into the dorso-rostral part of the neostriatum was a statistically significant stimulation at the highest doses (80 and 160 μg/side) during the last time interval (6–9 min) in comparison with the performance of saline injected controls. 0–3 min: $F(6,44)=0.67$, $MS_{error}=5.97$, n.s., 3–6 min: $F(6,44)=1.27$, $MS_{error}=9.85$, n.s., 6–9 min: $F(6,44)=3.75$ $MS_{error}=9.46$, $p<0.01$ (Fig. 6). There were no statistically significant effects on the number of rearings at any dose of DA (5–160 μg/side), $F(8,52)=0.78$, $MS_{error}=9.78$, n.s. (Fig. 3). The animals displayed normal coordinated movements and there was no complete disruption of habituation by the doses causing locomotor stimulation (80 and 160 μg/side). The duration of the effect was less than 30 min.

Effects of l-noradrenaline (l-NA). The bilateral administration of *l*-NA, 10–80 μg/side, into the neostriatum produced a very marked and statistically significant suppression of the locomotor activity, 0–3 min: $F(4,26)=14.53$, $MS_{error}=4.65$, $p<0.001$, 3–6 min: $F(4,26)=4.25$, $MS_{error}=5.75$, $p<0.01$, 6–9 min: $F(4,26)=1.37$, $MS_{error}=7.15$, n.s., (Fig. 7) and the number of rearings, $F(4,26)=15.38$, $MS_{error}=3.88$, $p<0.001$ (Fig. 3). No stimulation was obtained by the doses used within 9 min or later (30 min). When moving, the animals displayed normal coordinated movements. Although less marked than after injections into the nucleus accumbens, there were similar signs of discomfort (cf., above) in animals given 40–80 μg/side of *l*-NA. An additional group of animals was given 160 μg/side. The effects were similar to those seen after 80 μg/side and no locomotor stimulation was obtained. One of the 4 animals given the highest dose died in seizures.

DISCUSSION

The most conspicous effect of DA locally applied into the nucleus accumbens (10–160 μg/side) of normal rats is a suppression of the initial (0–3 min) intense exploratory activity in the open field. In addition, the highest doses (80 and 160 μg/side) also produced a stimulation of the locomotor activity at later time intervals. However, Pijnenburg *et al.* [25], using habituated rats, reported an increase in locomotor activity upon administration of low doses of DA in the nucleus accumbens and the experiments by Wachtel *et al.* [36] 2.5–10 μg of DA were found to stimulate locomotor activity 6–9 min but no 0–3 min after placement of the animals in the activity arena. These findings suggests the possibility that the effects of DA, locally applied to the nucleus accumbens, could be dependent on the initial level of locomotor activity (e.g., [30]). We have investigated this possibility in a separate experiment. Under the present experimental conditions, however, we found no evidence for an increase in activity in habituated rats by a low dose of DA (20 μg/side) into the nucleus accumbens. During the initial 3 min in the open field arena, the naive animals displayed an activity of 10.0 $\sqrt{x}$ counts/min and habituated animals 2.0 $\sqrt{x}$ counts/min. Following the local application of 20 μg of DA into the nucleus accumbens both naive and habituated animals decreased their locomotor activity (5.8 and 0.9 $\sqrt{x}$ counts/min respectively) and the effect produced by this dose of DA in naive animals is statistically significantly different from the effect produced in habituated animals ($p<0.01$). Thus we found no evidence for an increase in the locomotor activity after the application of DA at low doses in habituated rats.

The sedation produced by DA is most likely due to a preferential action at dopaminergic autoreceptors. In support of this it has been shown that systemic administration of the DA receptor agonist apomorphine [4,9] produces a suppression of locomotor activity in mice concomitant with a decrease in brain DA synthesis [31]. The ability of apomorphine to reduce DA synthesis and release is in all probability due to an agonist action at DA autoreceptors in the terminal area [12,18]. Furthermore, a direct application of apomorphine to the nucleus accumbens in the rat produces sedation [35]. However, there is evidence that, in the rat, nucleus accumbens efferents are inhibitory with respect to locomotor activity [13, 17, 22, 23, 38] and it has been reported that a lesion in the ventral tegmentum, containing the A10 DA cell area innervating i.a., the nucleus accumbens, produces hyperactivity in rats [15, 21, 28, 34]. Thus there is a possibility that also the postsynaptic effects of DA after local application to the nucleus accumbens may contribute to the suppression of locomotor activity in the rat.

Under the present experimental conditions there was a striking similarity in the effects produced by DA and *l*-NA when applied to the nucleus accumbens. Both catecholamines produced a suppression of locomotor activity followed by an increase in activity and a decrease in the number of rearings. There were no measurable differences in efficacy but *l*-NA was about four times as potent as DA in producing the effects. The pattern of activity within the open field arena (time spent at the wall vs. time spent in the center) was similar and not statistically different between the experimental groups and in comparison with controls (data not

shown). Thus using the different observations obtained, including pattern of within-session habituation, horizontal locomotor activity, vertical activity (rearing) and pattern of activity within the open field arena, the two treatments were qualitatively indistinguishable from each other.

In previous experiments it has been shown, using nialamide-pretreated rats, that the hyperactivity produced by *l*-NA in the nucleus accumbens is blocked by the DA-receptor blocking agents haloperidol or fluphenazine [1] indicating actions of the administered *l*-NA via dopaminergic mechanisms [8,26]. It is not likely however, that the effects of *l*-NA in the present experiments are mediated indirectly since *l*-NA was more potent than DA. Results from the experiments where *l*-NA and DA were applied locally into the neostriatum are also of interest in this regard. In this experiment both *l*-NA and DA produced statistically significant but opposite effects on the locomotor activity. There were some effects also after the administration of *d*-NA to the nucleus accumbens, although less marked in comparison with the effects produced by *l*-NA or DA. According to Jackson *et al.* [16] these effects may be mediated via a stimulation of DA receptors by *d*-NA. However since both DA and *l*-NA produced essentially the same effects after application to the nucleus accumbens, results from the present experiments do not allow such a comparison.

In contrast to the effects obtained by the local application of DA and *l*-NA into the nucleus accumbens there were important differences in the responses obtained by the two treatments in the neostriatum. *l*-NA produced a suppression of the locomotor activity at doses of 20–80 μg/side whereas no suppression of activity was found after DA in doses up to 160 μg/side. The only effect produced by DA was a stimulation of the locomotor activity at higher doses (80–160 μg/side). No stimulation of activity was seen after any of the doses of *l*-NA used. Furthermore, the number of rearings were markedly reduced by *l*-NA (20–80 μg/side) whereas no significant effects were obtained by DA at any dose (5–160 μg/side).

There is evidence that the nucleus accumbens is of great importance in the mediation of locomotor activity and plays a minor role for the occurrence of stereotyped behavior after administration of dopaminergic agonists systemically or locally, whereas the opposite is true for the neostriatum [6, 10, 14, 16, 19, 27]. This distinction is supported in the present experiments insofar as DA produced a suppression of locomotor activity in the accumbens but not in the neostriatum. However, high doses of DA produced a stimulation of activity to the same degree in either structure.

The failure to find any marked effects of NA in some of the previous studies may be due to the concomitant use of reserpine and/or nialamide [7, 16, 27]. In fact the α-receptor stimulating agent clonidine [2] does not reverse reserpine-induced suppression of locomotor activity. However, when given in combination with apomorphine, there is a further stimulation of activity indicating the importance of dopaminergic mechanisms in clonidine-induced stimulation of locomotor activity [5]. There is also biochemical evidence for interactions between NA and DA neurons (e.g., [3,24]) and it is possible that effects produced by NA depend on an intact dopaminergic neurotransmission. Furthermore, the potentiation of DA or NA effects by the use of MAO inhibitors may have prevented the observation of the locomotor suppression seen in the present experiments.

As part of the limbic system the nucleus accumbens is supposed to be involved in the mediation of emotional behavior. It is of interest to note that an elevation of nucleus accumbens NA (as well as in other limbic forebrain areas) has been shown in post-mortem studies on brains of patients with chronic paranoid schizophrenia [11]. It remains for future experiments however, to demonstrate how nucleus accumbens NA is further involved in the mediation of behavioral manifestations of the rat or other species.

In conclusion, the major effects of NA or DA locally applied to the nucleus accumbens of the rat is a suppression of exploratory locomotor activity followed by a stimulation when very large doses are administered. It is not possible to distinguish qualitatively the effects produced by NA from those produced by DA on the basis of separate recordings of the number of rearings or the pattern of locomotion within the open field arena. When administered to the neostriatum, locomotor stimulation is produced by DA whereas NA produced a suppression of the locomotor activity. The results indicate that both NA and DA may be involved in the mediation of exploratory locomotor activity in the rat and gives an example of a conjoint action of the two catecholamines in the nucleus accumbens.

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