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Effects of Intraaccumbens Microinjections of Quinpirole on Head Turning and Circling Movement in the Rat

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CRESCIMANNO, G., A. EMMI AND G. AMATO. *Effects of intraaccumbens microinjections of quinpirole on head turning and circling movement in the rat.* PHARMACOL BIOCHEM BEHAV **60**(4) 828–834, 1998.—This study was designed to evaluate whether nucleus accumbens dopamine D_2 receptors are involved in the initiation of the movement, as distinguished from its execution. For this purpose, the effects of the quinpirole-induced increase of nucleus accumbens dopamine D_2 receptor activity were observed on specific parameters of the circling behavior and of its first stage, the head-turning (HT) movement. The experiments were performed on rats with unilateral 6-hydroxydopamine (6-OHDA) lesion of the pars compacta of the substantia nigra and *d*-amphetamine IP (3 mg/kg). Bilateral intraaccumbens microinjections of quinpirole (1, 5, and 10 μg/0.5 μl), an agonist of the D_2 receptor family, were performed on three groups of animals. Bilateral saline (0.5 μl) was injected in a fourth group as control. An additional control experiment, with quinpirole (10 μg/0.5 μl) bilaterally injected in accumbens without *d*-amphetamine IP, was also performed in a further group of 6-OHDA–lesioned animals. By means of a videoanalysis system, HT duration, angle, and speed were analyzed. Modifications of the circling rate (increase), HT duration (decrease), HT angle (decrease or increase according to the dose), and HT speed (increase) were observed. Moreover, a very close head-to-tail position and a very short-diameter type of turn were also evidenced. Similar modifications, even if different in amplitude and in % distribution, were observed following bilateral quinpirole in accumbens without *d*-amphetamine IP. The results indicate a close relationship among head-turning speed, type of turn, and position of the animal in the circling motor sequence. We conclude that D_2 receptor family in nucleus accumbens is involved in the initiation of movement as distinguished from its execution. © 1998 Elsevier Science Inc.

Nucleus accumbens D_2 receptors Quinpirole Circling Head turning Sensory–motor integration Rat

THE nucleus accumbens (NAc) has been suggested to represent an interface between limbic and striatal systems (15,25), and has been implicated in a wide range of functions, like motor activity (9,10,14,22), reward (21,23,26), and attention (4,28). Different neurotransmitters influence accumbens activity (29), although many data suggest that dopamine plays a central role in high level functions (11,15,26). Moreover, dopaminergic (DA) D_2 receptor population has been shown to be both widely expressed in NAc (2) and involved in sensory–motor integration functions (3,25). However, some major issues are not currently resolved; among them, to what degree this receptor population may be concerned with strictly motor function vs. sensory function or vs. the integration of the two. In particular, still open is the question on whether NAc D_2 receptors are involved in the initiation of movement as distinguished from its execution. The most suitable animal model, to shed light on this matter, is the circling behavior, a fixed motor pattern consisting of stages, in which the initiation of the movement is distinct from its execution. This stereotyped, rotatory activity can be obtained in the rat by unilateral 6-hydroxydopamine (6-OHDA) lesion of the pars compacta of the substantia nigra (SNpc) and amphetamine IP (30). Previous studies have shown that circling behavior is composed of different, fixed, and detectable stages with the head turning (HT) movement considered as the first (8,19). The HT itself can be considered as a fixed and measurable motor pattern, in which sensory–motor integration processes play a critical role influencing specific parameters of the

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whole rotatory activity. In fact, the directional biases observed in rat locomotion, following unilateral dopamine depletion, have been explained to depend on a possible modified responsiveness to sensory stimulation or motor ability (6).

In addition, a relationship between indices of behavioral asymmetries and neurochemical changes, following 6-OHDA nigrostriatal lesions, has been evidenced (27).

In the present study, we investigated the effects of the activation of D_2 receptor family in NAc both on HT (initiation of the movement) and on circling (execution of the movement). For this purpose, in rats forced to circle after unilateral lesion of the SNpc and *d*-amphetamine intraperitoneal (IP), the bilateral microinjection in NAc of quinpirole, an agonist of the D_2 receptor family (D_2–D_3), was performed.

A subtle frame-by-frame video analysis was, thereafter, used to analyze HT and circling modifications.

METHOD

Animals

The experiments were performed on male Wistar rats, weighing 250–300 g. The animals were maintained on 12 L: 12 D cycle (light 0700, off 1900 h) in a temperature-controlled room (21°C), with free access to food and water. The observation was performed during the light phase of the day–night cycle.

Surgery

Thirty minutes before surgery, animals received an injection of imipramine hydrochloride (Research Biochemicals International, Natick, MA) (15 mg/kg IP) to prevent the neurotoxic effects of 6-OHDA on noradrenergic neurons.

Under ketamine (Ketalar, Parke-Davis, Milano, Italia) anesthesia (130 mg/kg IP), the animals were placed in a stereotaxic apparatus (DKI 1404). Holes were drilled in the skull and 6-OHDA (Research Biochemicals International), was unilaterally infused in SNpc (A −4.8–5.3; L 1.5–2.0; V 7.5–8.0) (18) via a 30-gauge stainless steel cannula connected by a polyetilene tubing to a 10 μl Hamilton microsyringe pump. Stainless steel 24-gauge guide cannulae (1 cm long) were bilaterally implanted into the NAc (A +2.2–2.7; L 1.5–2.0; V 6.5–7.0) 2 mm above the structure to avoid its damage.

Removable wire stilets were placed in the cannulae to prevent occlusion. Small crews were inserted into additional holes in the skull and dental acrylic cement (Paladur-Kultzer Gmbh, Wehrheim, Germany) covered the surface. An antibiotic powder (Kemicetine, Carlo Erba, Milano, Italia) was topically applied to the wound. Animals were tested after 1 week recovery period.

Drugs

6-OHDA (4 μg in 2 μl of a solution containing 0.2 mg/ml ascorbic acid), delivered at a rate of 1 μl/8 min, was unilaterally infused (total injected volume 2 μl) in the SNpc. One week postsurgery, the rats received drug microinfusions by 30-gauge injection needles, extending 2 mm beyond the tip of the cannula and connected to a Hamilton microsyringe automatically pushed by a pump (model Razel A-99), delivering the drug at a rate of 0.5 μl/4 min. Quinpirole (Research Biochemicals International), dissolved in saline, was bilaterally and simultaneously injected in NAc, 0.5 μl for each side. The control consisted of bilateral injection in NAc of 0.5 μl of vehicle solution plus *d*-amphetamine IP Bilateral infusions were employed because in our experimental model, being the animal was unilaterally lesioned, it presented a DA asymmetry between the two sides. Therefore, bilateral drug microinfusions avoided any further increase of DA imbalance.

Infusion time was 4 min, and the injectors remained in the cannulae 1 more min to allow diffusion of the drug. Then, new sterile wire stilets were inserted. Previous analyses demonstrated that these injection procedures resulted in minimal tissue damage beyond the injector tip.

After the intracerebral injection, *d*-amphetamine (Sigma Chemical Company, St. Louis. MO), dissolved in saline, was injected IP (3 mg/kg).

Apparatus

The experiments were performed in a sound-attenuating room. The apparatus consisted of a perspex observation box (30 × 30 × 30 cm) illuminated by a 4-W neon tube and ventilated by a noiseless fan. The experimental trials were recorded by a video camera apparatus (video camera Bauer VCC 550 AF SVHS) and afterwards analyzed by a videocassette recorder (JVC HR-S6800E SVHS).

Behavioral Analysis

Twenty-four hours before the beginning of the trials the animals were placed in the experimental box and subjected to habituation to the novel environment. On the test day, animals were set in round plastic tubs (30 cm diameter) to minimize locomotor activity, and bilaterally injected into NAc. Then, they received *d*-amphetamine IP and were observed for 1 h.

Only those rats showing full turns ipsilateral to the lesioned side, after *d*-amphetamine IP and intraaccumbens saline or quinpirole, were considered in our study.

The fixed motor pattern was studied on playback in slow motion and pause–still, which allowed stopping or moving forward single frames every 40 ms. With the aid of this apparatus, the different parameters of the motor sequence, recorded frame by frame, could be evaluated. We recorded and measured initial and final frames corresponding to initial and final positions of the animal's head. Thanks to the analysis of both initial and final frames, HT duration, angle, and speed were calculated. HT initial time was calculated taking into consideration the frame preceding the start of the head rotatory movement, whereas final HT time was considered to occur at the frame preceding the start of the body movement in the circling motor sequence. The interval between the initial and the final time was the HT duration.

The rats were tested once only, using 10 animals for each quinpirole dosage (1, 5, and 10 μg) and 10 for saline as control.

Two behavioral analyses were performed: (a) animal activity was observed for 1 h, taking into account number of turns, type of circling and animal's position; (b) the initial and final positions of the head were recorded and measured to determine HT duration and angle.

To exclude that an activation of striatal dopamine D_2 receptor, after the use of the larger dose of quinpirole (10 μg/0.5 μl), could contribute to the changes of HT angle observed, an additional control experiment with bilateral quinpirole in accumbens without *d*-amphetamine IP, was also performed in 10 animals, unilaterally lesioned in the SNpc with 6-OHDA. One week postlesion, the animals were subjected to habituation. The following day, the analysis of the already described

circling and HT parameters was carried out for the preinjection period of observation. After 24 h, the animals were bilaterally injected with quinpirole in accumbens.

Histology

At the end of the experiments, the animals were deeply anesthetized and perfused with saline followed by 10% formol-saline solution. Position of the canula tips in NAc and extent of the lesion in SNpc were checked on serial Nissl sections (Fig. 1).

Statistical Analysis

All data are presented as the means ± SEM, and the statistical analysis for differences between the control and the quinpirole-treated groups was performed using the one-way analysis of variance (ANOVA). Values of $p < 0.05$ were considered significant. For the 6-OHDA–lesioned animals, bilaterally injected with quinpirole in accumbens without *d*-amphetamine IP, the paired Student's *t*-test (two tailed) was used (p-values <0.05 were regarded as significant).

RESULTS

Bilateral microinjections in NAc of quinpirole and *d*-amphetamine IP resulted in a dose-dependent increase of ipsilateral circling rate (control condition 341.57 ± 16 turns); with 1 μg we observed 383.65 ± 47 turns, $F(1, 19) = 7.19$, $p < 0.015$; 421 ± 41, $F(1, 19) = 32.57$, $p < 0.0001$, with 5 μg, and 455.11 ± 16.44, $F(1, 19) = 43.55$, $p < 0.0001$ with 10 μg.

HT duration analysis showed a dose-dependent decrease in quinpirole injected rats (control condition = 0.59 ± 0.11 s). The effect was not significant for the dosage of 1 μg (HT duration = 0.55 ± 0.10 s), $F(1, 19) = 0.72$, $p < 0.4$; whereas, significant effects were observed for 5 μg (HT duration = 0.43 ± 0.06 s), $F(1, 19) = 16.31$, $p < 0.0001$, and for 10 μg (HT duration = 0.33 ± 0.05 s), $F(1, 19) = 46.30$, $p < 0.0001$ (Fig. 2A).

HT angle was calculated for each quinpirole dosage, taking into account the initial and final position of the animal's head. With the dosage of 1, 5, or 10 μg, the results were respectively: 40°, 47°, and 36°; the control condition value was 47° (Fig. 2B).

Quinpirole microinjection provoked a weak and nonsignificant increase of HT angle with the lowest dose, $F(1, 19) = 2.24$, $p < 0.15$. Intermediate dose provoked the same HT an-

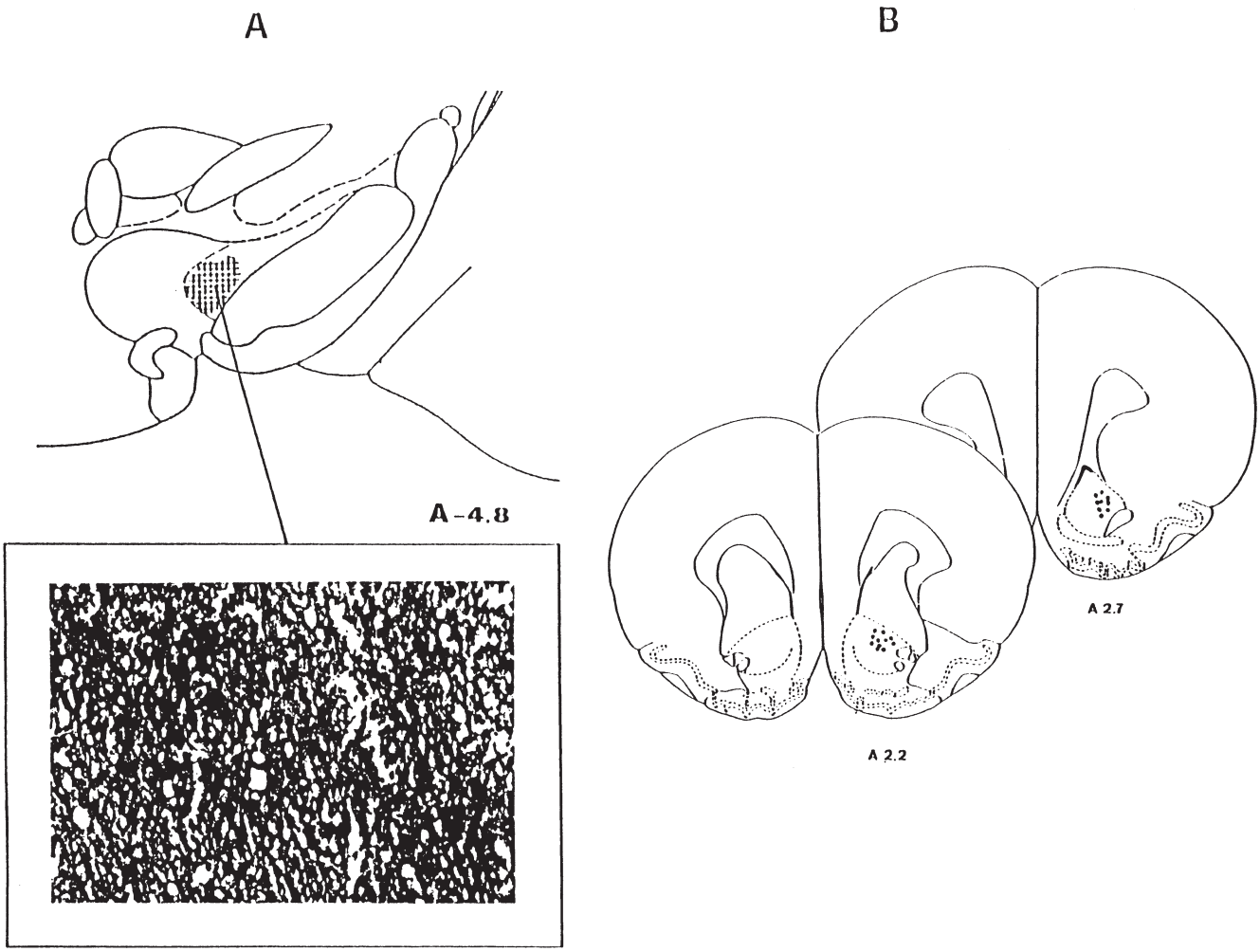

FIG. 1. (A) Schematic representation of SNpc lesion (hatched area), following 4 μg/2 μl injection of 6-OHDA (1 μl/8 min) and higher magnification (×190) of the lesioned area (cresyl violet). (B) Reconstructions of injection sites into nucleus accumbens, shown on two coronal sections of the brain. Stereotaxic planes are from the atlas of Paxinos and Watson, distances are in mm from the bregma.

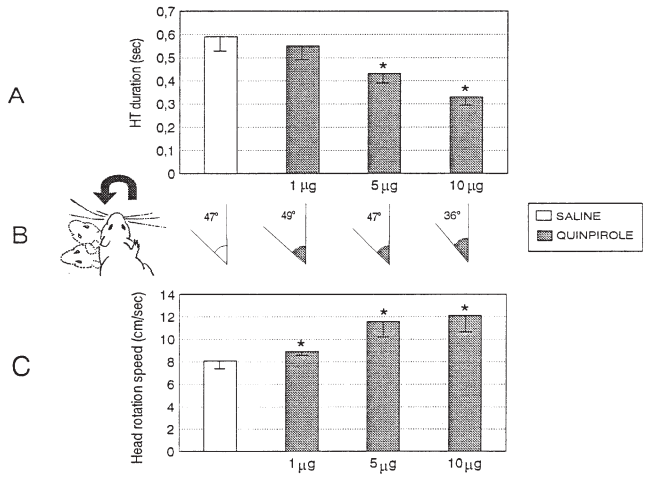

FIG. 2. In rats, unilaterally lesioned in the SNpc with 6-OHDA, the effects of bilateral microinjections into NAc of saline (0.5 μl) or quinpirole (1, 5, or 10 μg/0.5 μl) and *d*-amphetamine IP (3 mg/kg) are shown. (A) HT duration, (B) HT angle, and (C) HT speed. HT movement is shown on the left side. Each value shows the mean ± SEM of the results obtained from the analysis of 10 animals. $*p < 0.0001$ (ANOVA).

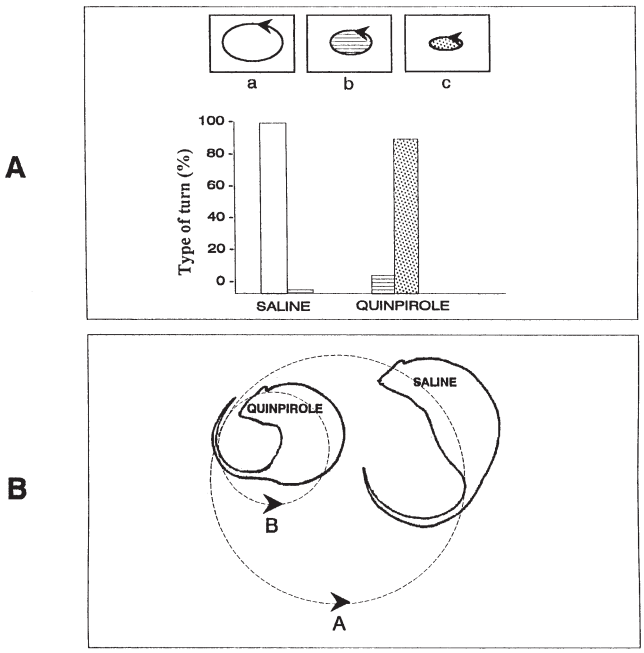

FIG. 3. (A) Percent distribution of different types of circling in rats unilaterally lesioned by 6-OHDA in SNpc, bilaterally injected into NAc with saline (0.5 μl, 10 animals) or quinpirole (10 μg/0.5 μl, 10 animals) and intraperitoneally administered *d*-amphetamine (3 mg/kg). In the upper inset, the different types of circling are shown: *a* = wide-diameter circling, *b* = short-diameter circling, *c* = very short-diameter circling. (B) Relationship between animal's position and type of turn (dotted circles). Same dosage as (A). Saline: close head-to-tail position and wide-diameter circling (*A* type of turn). Quinpirole: very close head-to-tail position and very short-diameter circling (*C* type of turn).

gle of the control, and the highest dose provoked a significant decrease of HT angle $F(1, 19) = 146.76$, $p < 0.0001$.

Following the analysis of HT angle (space) and of HT duration (time), the speed (space/time) of the head turning rotation was evaluated.

Quinpirole microinjections provoked a dose-dependent increase of HT speed. The statistical analysis showed significant effects for all the dosages employed (control condition 8.05 ± 0.44 cm/s). With the dosage of 1 μg the speed was 8.90 ± 0.30 cm/s, $F(1, 19) = 25.48$, $p < 0.0001$; with 5 μg was 11.56 ± 0.85 cm/s, $F(1, 19) = 134.48$, $p < 0.0001$; and with 10 μg was 12.10 ± 0.92 cm/s, $F(1, 19) = 144.58$, $p < 0.0001$ (Fig. 2c).

Modifications of the type of circling and of the animal's position have been also analyzed.

Wide diameter turns (*a* type of turn, 97% of the observations) and short-diameter turns (*b* type of turn, 3% of the observations), characterized the control condition. Whereas, very short-diameter turns (*c* type of turn, 90% of the observations) and short-diameter ones (*b* type of turn, 10% of the observations) were observed, following quinpirole in NAc (Fig. 3A). This effect was present for all the dosages.

The study of the animal's position showed a relationship between the very short-diameter circling and the very close head-to-tail position, in the quinpirole-treated rats. In control condition, wide-diameter circling related to a close head-to-tail position appeared (Fig. 3B). These evidences did not change with different dosages of the drug.

The group of 6-OHDA–lesioned animals, treated with bilateral accumbens microinjection (10 μg) without *d*-amphetamine IP, showed a rotatory activity ipsilateral to the lesioned side. When compared to the preinjection period of observation, the circling rate significantly increased from 23.90 ± 2.28 to 45.50 ± 3.63 turns [paired *t*-test, $t(9) = -5.644$, $p < 0.0001$] even if the total number of turns observed during 1 h was less, with respect to the one observed in the animals administered *d*-amphetamine IP. HT duration and HT angle significantly decreased from 0.70 ± 0.03 to 0.56 ± 0.02 s [paired *t*-test $t(9) = 5.845$, $p < 0.0001$], and from 52° to 43° [paired *t*-test, $t(9) = 19.624$, $p < 0.001$], respectively. HT speed significantly increased from 6.97 ± 0.17 to 9.11 ± 0.19 cm/s [paired *t*-test, $t(9) = -10.156$, $p < 0.0001$].

The small number of turns observed during the preinjection period were characterized by wide-diameter turns (*a* type of turn, almost 100% of the observations). Very short-diameter turns (*c* type of turn, 92% of the observations), and short-diameter ones (*b* type of turn, 8%) were present in the animals bilaterally injected with quinpirole in accumbens.

A weak body deviation toward the lesioned side characterized the animal position during the preinjection period of observation. After quinpirole, the position ranged from the close head-to-tail (34% of the observations) to the very close head-to-tail one (66%).

DISCUSSION

The ability to analyze specific parameters of an initial act, in the chain of stages characterizing the rotational behavior, has been useful in deciphering a role for NAc D_2 receptors in the initiation of movement as distinguished from its execution.

Our data suggest that activation of D_2 receptor family in NAc provoked a specific influence on the initiation of the movement. We observed a dose-dependent, significant increase of HT speed and number of turns. Moreover, very short-diameter turns and a very close head-to-tail position

characterized the behavioral responses of the animals to intraaccumbens quinpirole. However, the parameter all the others mainly depended on was the HT speed. In fact, to the increase of HT speed corresponded both the decrease of the turn diameter and the very close head-to-tail position of the animal.

In the attempt to explain our results, it is necessary to consider that, if on the one hand, the dorsal striatum has been attributed a role in the direction of rotation and the ventral striatum a role in mediation of locomotor activity (20), on the other hand, the NAc has been supposed to be an interface between limbic and striatal activities, directed to modulate sensory–motor integration processes (15,25). According to this point of view, the activation of D_2 receptor family in NAc might influence the head–body motor coordination. In fact, a dose-dependent decrease of HT duration and modifications of HT angle were observed. This last evidence seems not to depend on an increased difference in dopamine transmission between the intact and the lesioned striatum, triggered by a possible diffusion of the drug. In fact, very small or no differences were observed in this respect between saline (angle 47°) and quinpirole treated rats at 1 and 5 μg (angles: 49° and 47°, respectively).

The additional control, carried out using bilateral accumbens microinjection of the larger dose of quinpirole without *d*-amphetamine IP, resulted in significant modifications of HT duration and angle. This evidence contributes to exclude that the possible diffusion of quinpirole into the striatum, inducing a head turning in the opposite side from the one induced by *d*-amphetamine, could therefore give account for the reduction of HT angle. More likely, the variations of the angles may be due to the increase of HT speed, which leads to the impossibility in performing a whole-head rotation; therefore, an influence on the initiation of body movement, which could be more quickly triggered, because of an anticipated reaching of the animal's head final position, might be hypothesized.

Regarding the changes of the type of turn and position of the animal, previously observed by Ziegler and Szechtman (34), they can be explained according to the hypothesis concerning a functional link between modifications of the trajectories and modifications of thigmotactic scanning (27). NAc D_2 receptors may influence thigmotactic function, likely by regulating the incoming of sensory information from the environment. This interpretation is supported by studies concerning responses of single NAc units to somatosensory stimuli (32). The pharmacological manipulation of NAc might, therefore, specifically affect the motor response to environmental stimuli.

The changes of the body curvature might have been secondary to the effects of the drug on head-turning angle. However, the smaller diameter turn was seen with all the three doses of quinpirole used, whereas the HT angle after 1 and 5 μg was either higher or similar to the control group one, respectively. This implied that the diameter of the turn was not dependent on the HT angle. An interesting point of view on this issue has been proposed by Miklyaeva et al. (17). They focused their attention on limbs of the affected side in the lesioned animals, which may be unable to apply force to adjust posture and produce movement. Quinpirole in NAc might overburden this condition, thus provoking the very close head-to-tail position. On the other hand, very short-diameter turns and very close head-to-tail position might constitute the behavioral correlate of the dopamine-dependent ventral striatum modulation of the cortico-strio-nigro-thalamo-cortical feedback circuit (1). A support to this hypothesis has been given by recent data, concerning a topographical and electrophysiological relationship between prefrontal cortex and specific region of the NAc related to substantia nigra (16).

The increased circling rate, observed in our experiments, on the one hand may depend on specific changes of HT and circling parameters (e.g., increase of HT speed and decrease of turn diameter) as demonstrated by the results obtained in the animals in which quinpirole was injected in NAc without *d*-amphetamine IP. On the other hand, an increase in motor activity, due to the facilitation of the DA transmission in NAc (9,12,13), is to be considered. In fact, the dopamine released in NAc can influence the motor system by acting on the SN (5) or suppressing the inhibition from the amygdala to the ventral pallidum via a presynaptic modulatory action (33). In addition, modifications of HT, and a decrease of the circling rate, following sulpiride microinjections into NAc (i.e., following D_2 receptor blockade), have been recently shown in the rat (7,8). Interestingly, it has been suggested that dopamine in accumbens might modulate the ability of neocortical and limbic areas in influencing complex aspects of sensory–motor function (15,25). Our data strengthen this point of view, showing that activation of D_2 receptor family in NAc provokes specific modifications of HT parameters, likely linked to sensory–motor integration activities. However, considering the data concerning potentiated responses produced by coactivation of both D_1 and D_2 receptors (24,31), a synergistic interaction seems to be likely. In conclusion, because an influence of NAc on the mechanisms linked both to sensory and motor control has been shown, it is possible to suggest that D_2 receptor population in NAc may be involved in the control of specific parameters of the initiation of the motor response to environmental stimuli.

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