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D_2-agonist quinpirole induces perseveration of routes and hyperactivity but no perseveration of movements

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The behavior in an open field of rats injected with the D_2-agonist quinpirole (2 mg/kg; $n = 10$) and saline ($n = 10$) was analyzed in terms of routes and movements. Quinpirole induces perseveration of routes without inducing perseveration of movements. Perseveration of routes consists of repeated travel along a few paths in a limited portion of the environment. Lack of perseveration of movements was evidenced by the same distribution of lateral, vertical, and forward movements as in saline-treated animals. Quinpirole also increased the total amount of progression and the total number of movements performed by the rat's body parts along all dimensions of movements. Thus, under quinpirole, animals were hyperactive, stereotyped in route, but free in movement. This profile resembles behavior under low doses of amphetamine but not the behavior under either apomorphine or high doses of amphetamine. Thus, contrary to the current view, administration of a D_2-receptor agonist is sufficient to produce a major component of dopamine-induced stereotyped behavior. It is suggested that quinpirole induces perseveration of route by affecting presynaptic release of dopamine, and that the organization of route is independent of the organization of movement.

INTRODUCTION

The early notion that stereotyped behavior induced by dopamine agonists is produced by stimulation of D_2 receptors[7,32] has been recently challenged. Several studies conclude that concurrent stimulation of both D_1- and D_2-receptor subtypes is required to induce dopamine-mediated behaviors[2,23,24,29,30,36]. In these studies oral stereotypies are taken to be the sine qua non of dopamine-mediated stereotyped behavior. The present study shows that administration of the selective D_2-receptor agonist, quinpirole, is sufficient to produce a major component — hitherto largely ignored — of stereotyped behavior observed under less specific dopamine stimulants. This component consists of stereotyped progression along fixed routes.

Schiorring[31] provided systematic evidence that one component of amphetamine-induced stereotyped behavior is exaggerated and repetitive locomotion along fixed routes. This aspect of drug stereotypy has been later largely ignored, presumably because of lack of an appropriate technology of analysis. Such technology was recently introduced by Geyer et al.[17,18] who used the spatial distribution of routes traced by drug-treated rats to measure the degree of stereotypy induced by different drugs. Another technology was developed by Eilam and Golani[8–11]. These latter authors treat the rat's progression in the environment as a sequence of paths (routes) and places of stopping, and record those continuously. In addition, they record continuously the changes of relation between the parts of the rat's body (movements). In a recent application of this technology to the analysis of behavior under amphetamine, they demonstrate that low doses of amphetamine (0.5–1 mg/kg) induce hyperactivity and perseveration of progression along fixed routes in the environment, but do not have a discernible effect on the organization of movement. Higher

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doses (2.5–5 mg/kg), induce both perseveration of progression along long fixed routes, and perseveration of movement[8,11].

Unlike amphetamine, apomorphine, a mixed D_1/D_2-receptor agonist, induces perseveration of movement even at moderate doses[5,34] (about 1.25 mg/kg). Specifically during the course of its action, apomorphine induces successive elimination of vertical and forward movements, resulting in perseverative movement along the lateral dimension.

In the present study, the method and conceptual framework of Eilam and Golani[8–11] is used to examine the effects of quinpirole on behavior. The behavioral profile under quinpirole is then compared to that established for the less selective dopaminergic drugs.

MATERIALS AND METHODS

Animals

Twenty naive Long–Evans male hooded rats (Charles River, Canada), weighing 350–550 g at the time of testing, were housed in a temperature-controlled room (lights on: 07.00–19.00 h). Food and water were provided ad lib. Subjects were handled daily for at least a week before the study.

Drugs

Quinpirole (LY171555; Lilly Research Laboratories) was dissolved in saline (2 mg/ml) and was injected s.c. in the nape of the neck at a concentration of 2 mg/kg. Pilot experiments suggested that the behavioral effects obtained at this dose were typical of the effects observed in the dose range from 0.125 to 8 mg/kg. Control rats received an equal volume of saline.

Apparatus

The open field is described in detail elsewhere[10]. Briefly, it is a large glass table (160 × 160 and 60 cm high) without walls, placed at least 70 cm away from walls in an empty air-conditioned (18 °C) room. A mirror below the glass allows the TV camera to capture simultaneously a bottom and a side view of the rat. The open field is subdivided into 25 rectangular locales. We use the terms 'locale' and 'place' interchangeably.

The animal was videotaped from behind a curtain. The outside objects visible to the rat were 3 walls, the curtain, the TV camera, two 500 W photographic lights, the fluorescent lighting on the ceiling, and the head of the observer.

Procedure

Immediately after injection of quinpirole ($n = 10$) or saline ($n = 10$), animals were placed gently in the center of the open field, and filmed continuously for 2 h. Each rat was experimentally naive and tested once. Tests were performed during the light phase of the day–night cycle.

Analysis of routes and movements

As noted previously[8,10,11], in an open field a rat can be either locomoting or not. Periods of locomotion are referred to as periods of progression and periods of no locomotion as 'stops'. During forward progression rats do not perform large vertical or lateral movements, or activities such as grooming; such movements and activities are typically performed during stops. This spatio-temporal separation permits one to describe behavior in terms of a sequence of stops in specific places, and in terms of the movements performed in these places[8,10,11]. Behavior was scored during slow-motion playback of video records. For each rat, the entire 2 h period of observation was analyzed.

Routes. In animals injected with amphetamine[8,11], saline, or quinpirole, progression between 2 successive stops is typically along a relatively straight path. Consequently, a route is defined as the straight path connecting 2 successive stops, and the paths of progression can be reconstructed from the sequence of stops.

Movements. Movements are described using the framework and tools of the Eshkol–Wachman Movement Notation[15] (EW). Certain aspects of this system are sufficient to describe much of the structure of rat movements[8–11,19,20,34]. The procedure used in the present study is detailed in ref. 9. Briefly, the body of the rat is divided into 3 articulated body parts (head, upper torso, and lower torso). Movements of these parts along each spatial dimension are defined as follows: *lateral movement* is the change in orientation (position) of a body part in the horizontal plane, either clockwise or counterclockwise; *vertical movement* is the change in orientation

(position) of a body part in the vertical plane; *forward progression* is forward transport of the lower torso (and thus the whole body), accompanied by forward steps of all 4 legs.

In the present analysis, the duration and amplitude of movements were not considered, only the initiations of the movements were recorded. In addition, movements of only the head were scored as such, movements in which both the upper torso and the head change their location in space were scored as upper torso movements, and movements in which the whole trunk changes its location (i.e., pivoting, rearing and forward progression) were scored as lower torso movements (for a rationale of this scoring method, see ref. 9). Lateral movements of less than 22.5°, and minimal vertical movements that do not involve release of snout contact, were ignored. Unlike lateral and vertical movements, forward movements of the head and upper torso were not scored. Forward progression was measured in terms of the distance traversed, where the unit of distance is one rat body-length (excluding the tail; one rat body-length equals approximately 20 cm). Because forward progression involves the transport of the body from place to place, distance traversed is equivalent to the length of the paths of progression.

The present study does not include an analysis of simultaneous movements, which indicate another aspect of organization of movement, namely, the coordination among body parts.

Measures of spatial distribution

For statistical evaluation of the distribution of progression through space, we follow others[16,17] and computed for each rat the coefficient of variation of the frequency of stops in each locale, and of the frequency of each unique route. A high coefficient indicates relatively frequent stops in some places and rare stops in others; for routes, it indicates relatively frequent travel along one or several paths and rare travel along others. A low coefficient of variation indicates a relatively uniform distribution of stops or routes across the open field.

Statistics

Unless specified otherwise, statistical comparisons between saline and quinpirole groups were performed using *t*-tests. Criterion for statistical significance was $P < 0.05$ (two-tailed probability). In the analyses of variance on percentage scores, the group effect is not considered because the means of the saline and quinpirole groups are both necessarily equal to 100%.

RESULTS

As stated in Materials and Methods, the behavior of rats in an open field is comprised of an alternation between periods of progression and stops[10]. Progression refers to the transport of the body along its longitudinal axis through the successive stepping of all 4 legs forward. Progression is interrupted by stationary periods in which the animal remains in the same locale. Any period, short or long, in which the animal remains at a place (locale), is termed a 'stop' or a 'visit', the terms being interchangeable. While stopping at a locale, the rat performs movements such as rearing (vertical movements of the lower torso), grooming, lateral head movements, and pivoting (lateral displacement or turning of the lower torso without forward progression).

Using this framework, the effect of the drug can be either on forward progression, stops, or the specific movements that the animal performs. Below, we examine the effect of quinpirole on the distribution of stops, on the routes, and finally, on movements.

Incidence and distribution of stops

In the 2 h of open field observation, rats injected with quinpirole made significantly more stops than animals injected with saline (320.7 ± 89.4 vs 81.3 ± 17.6 stops, $P = 0.017$). Since drug-treated rats stopped more often, it might be expected that they visited all places in the open field more frequently. However, the higher incidence of stops was a reflection of more frequent visits to only a few locales. This is evident from the data presented below.

To ascertain the spatial distribution of visits, for each rat the number of visits to each of the 25 places in the open field was calculated, and the frequency of visits was sorted from highest to lowest. The mean number of visits for each rank-ordered frequency was then computed for the saline and quinpirole

groups. Fig. 1A summarizes the results. Inspection of the figure suggests that for saline animals, the spatial distribution of visits was relatively uniform, indicating low, but more or less equal numbers of visits to almost every place in the open field. In contrast, for quinpirole animals, the distribution of visits followed a negative exponential shape, indicating an exaggerated concentration of visits to only a few places. Thus, under the drug, 50% and 90% of all visits were, on the average (± S.E.M.), to only 2.36 ± 0.20 and 7.85 ± 0.92 locales, respectively. Under saline, on the other hand, the corresponding numbers were 4.92 ± 0.53 and 13.99 ± 1.25 locales (Fig. 1A, inset). This confinement of visits to fewer places under quinpirole was statistically significant ($P < 0.001$ and $P = 0.001$ for number of places comprising 50 and 90 percent of all visits, respectively). The more limited spatial distribution of visits is reflected also in the statistical finding of a significantly greater mean coefficient of variation for number of visits per place in drugged animals compared to animals injected with saline (1.7873 ± 0.143 vs 1.0238 ± 0.117, $P = 0.001$). It appears, therefore, that while quinpirole elevated the number of stops, it also restricted their spatial distribution, confining most to just a few places.

Although only a few places were visited frequently, they were not necessarily the same ones for different animals. Inspection of frequency of visits to each of the 25 places in the open field, revealed that while every animal (and especially the ones treated with quinpirole), visited several places exceedingly more frequently than other locales, the location in the environment of the preferred spots varied from animal to animal (data not shown). Therefore, it seems unlikely that the observed preference is a reflection of some intrinsically attractive physical property of the place per se. Rather, it may reflect the assignment of a unique property to some place or places in the environment by the individuals themselves.

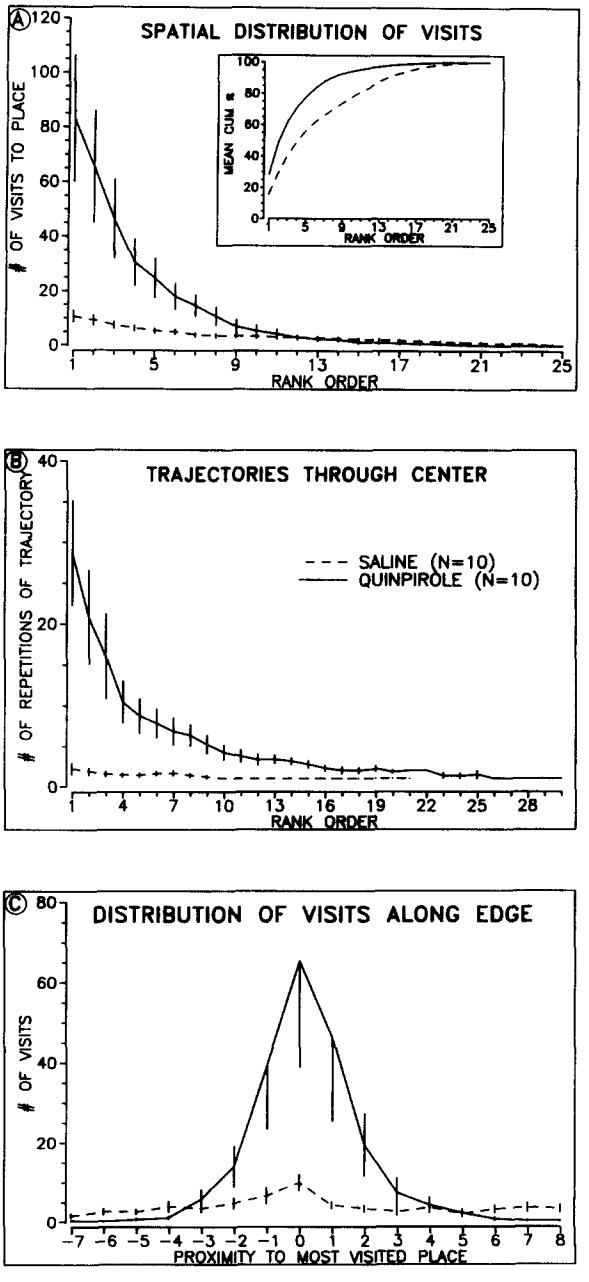


Fig. 1. Effect of quinpirole on 3 parameters of locomotion through the environment: number of visits to each of the 25 places in the open field (A); number of repetitions of each unique route passing through a central area of the open field (B); and, frequency of stops in locales along the edge (C). A 'stop' ('visit') begins whenever forward stepping is interrupted by a closing step. In making a closing step, the stepping fore- or hindleg lands alongside the corresponding leg; during forward locomotion it lands ahead of the other leg, shifting the animal's weight forward. Number of visits and frequency of repetitions are sorted from highest to lowest. Stops along the edge are aligned with respect to the most visited place (0 on the X-axis); successive places to the right and left of it are assigned positive and negative numerals, respectively. Values are means ± S.E.M. Inset: same data as in (A) expressed as cumulative percentage of visits. (The graph illustrates that under quinpirole rats visited a few places excessively, used a few routes through the center repeatedly, and stopped along the edge in only a few closely adjacent locales.)

Routes

In the 2 h of observation, rats injected with quinpirole locomoted significantly more than animals injected with saline (652.0 ± 192.1 vs 219.9 ± 49.1 units of body length, $P = 0.043$). In two respects, however, their paths of locomotion differed from the pattern shown by animals injected with saline. First, saline animals were unlikely to cross the center of the open field whereas animals injected with quinpirole traversed the center repeatedly. Second, saline animals were likely to move all around the periphery of the open field but animals injected with quinpirole moved along only a portion of the periphery. These observations are illustrated graphically in Fig. 2 and are supported by the following quantitative analysis.

To examine locomotion through the central area of the open field, the sequence of stops was determined for each rat. The line connecting two successive stops is equivalent to the route of progression between the two places. For each route, we noted whether it was along the edge or whether it departed from the periphery, entering or crossing the central area of the field. The frequency of each unique route through the central area was calculated, and sorted from highest to lowest for each rat. The mean of each rank-ordered frequency was then computed for the saline and quinpirole groups. Fig. 1B summarizes the results. Inspection of the figure reveals two points. First, it shows that animals injected with quinpirole passed through the central area significantly more frequently than animals treated with saline (136.5 ± 31.9 vs 14.9 ± 4.3, $P = 0.001$). Moreover, the proportion of their paths

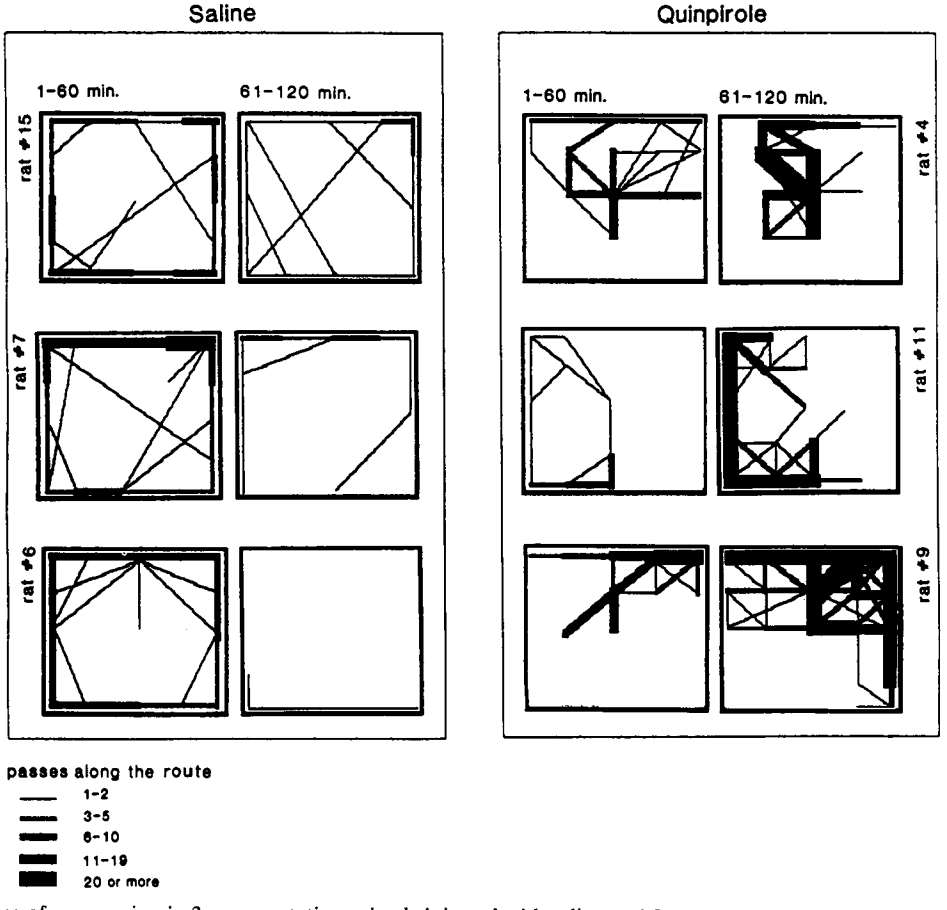


Fig. 2. The routes of progression in 3 representative animals injected with saline and 3 representative rats injected with quinpirole. The thicker the route, the more often the animal locomoted along it. For each rat, the routes of progression are shown separately for the first and the second hour of observation.

through the center (out of the total number of paths exhibited) was also significantly elevated (61.0 ± 11.3% vs 23.3 ± 7.0%, $P = 0.011$). Second, it indicates that of the many possible routes through the center, quinpirole animals selected only a few, moving along them repeatedly. In contrast, animals injected with saline rarely used the same central route twice. This difference in the spatial distribution of routes through the central area is reflected in the statistical finding of a significantly greater mean coefficient of variation for frequency of paths in drugged animals compared to animals injected with saline (1.1073 ± 0.123 vs 0.2630 ± 0.096, $P < 0.001$). Thus, quinpirole elevated the number of times animals entered the center but, at the same time, it also restricted their progression to repeated travel along a few routes only.

To examine the pattern of progression along the edge (periphery) of the open field, we used an indirect approach and calculated the number of times the animal visited each of the 16 places on the edge of the field. For each animal, the most visited place was assigned position 0, the place to the right of it, position 1, and so on clockwise for each successive place along the edge up to position 8. Corresponding successive places to the left of the most visited place, were assigned position −1 up to position −7. To assess the spatial distribution of visits to the edge, the mean number of visits to each of those positions was calculated for the saline and quinpirole animals. Fig. 1C presents the results. It is readily apparent that animals injected with quinpirole visited almost exclusively only a few adjoining places along the edge. In fact, almost 90% (89.4 ± 3.2%) of all visits were made to only 7 adjacent places, indicating that the animals neglected to explore half of the border of the open field. In contrast, animals treated with saline visited not only all of the places along the edge, but explored each of them more or less with equal frequency (except for 2 places which were visited somewhat more often). The difference in the spatial distribution of visits along the edge by drug-treated and saline animals was statistically significant, as assessed by comparing their coefficient of variation for frequency of visits along edge (1.5856 ± 0.126 vs 0.9692 ± 0.189, $P = 0.014$), or the percentage of all visits to 7 adjacent locations (89.4 ± 3.2% vs 61.8 ± 5.7%, $P = 0.001$). Thus, unlike saline animals which moved all around the border (edge) of the open field, animals injected with quinpirole locomoted along only a portion of the edge.

Therefore, the drug not only increased the amount of locomotion, but, at the same time, it also altered the topography of exploration by constricting the animal's exploratory space and confining its travel to a few routes only.

Distribution of activity during the course of drug action

The increased locomotion during the 2 h of testing under quinpirole was not present immediately after injection of the drug. On the contrary, locomotion was depressed at first and the rise in activity did not occur until approximately 60 min post-injection. This is evident from an inspection of Fig. 3A, which shows the time course of forward progression in successive 5 min intervals for rats injected with quinpirole and saline. The figure indicates that under the drug, the amount of forward progression was low in the first hour but relatively high in the second hour of observation; the peak in the amount of progression was reached at about 105–110 min after injection. The opposite occurred under saline. The amount of locomotion was highest immediately after injection, declined to low levels within half an hour, and remained at those low levels for the rest of the observation period. Thus, under saline, there was a shift from extensive locomotion to relative immobility while under quinpirole, there was a transition from relative immobility to extensive progression. These observations are supported by the following statistical analysis.

To facilitate statistical analysis, the data were collapsed into six 20 min bins (Fig. 3A, inset). A Group by Time analysis of variance with repeated measures on the Time factor, revealed a significant Group effect ($P = 0.043$) indicating, as noted above, that the amount of progression differed between quinpirole and saline groups. Moreover, the Group by Time interaction was also significant ($P < 0.001$), suggesting that the course of progression across time was different in the two groups. Individual comparisons at each of the 6 time points indicated that in the first 20 min interval, saline animals locomoted significantly more than quinpirole rats ($P = 0.049$)

and in the last 3 intervals the reverse was true ($P \leq 0.049$, Fig. 3A, inset). Since Fig. 3A suggested that the initial inhibition of locomotion under quinpirole was not present throughout the whole 20 min interval, the statistical validity of this observation was assessed by examining the first four 5 min intervals. These tests revealed that compared to saline, locomotion under quinpirole was significantly reduced in the first ($P = 0.006$) and second ($P = 0.049$) 5 min intervals only. Thus, under quinpirole (as compared to animals injected with saline), there is an initial inhibition, followed by an elevation of locomotion.

As shown in Fig. 3A, and Fig. 3A inset, in addition to increasing the mean amount of forward progression, quinpirole increased also the variance. Inspection of the data of individual animals, as well as of the video tape records, revealed that this variance reflects the fact that in some animals the amount of progression was unusually large and in

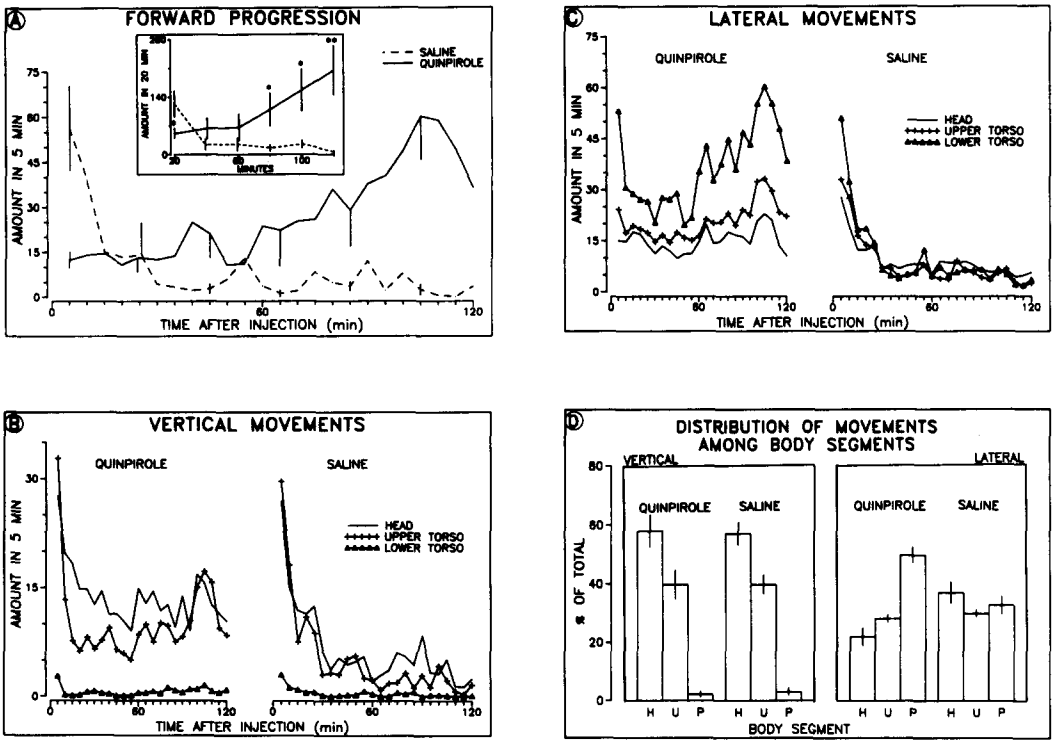


Fig. 3. Time course of the effect of quinpirole on forward (A), lateral (B), and vertical (C) movements of body parts (head, upper torso, and lower torso), and the proportion of vertical and lateral movements performed by each body part (D). For forward movements, only movements of the whole body (lower torso) are shown, and are equivalent to forward progression. The amount of forward progression is the length of the distance that the torso was transported, measured in units of one rat body-length (20 cm); for lateral and vertical movements, amount is the number of times the indicated body part initiated such a movement (see Materials and Methods). Each graph point corresponds to the mean amount of movements in the indicated 5-min interval. Data were obtained from continuous video records of rats' behavior and are a complete summary of 2 h of activity. In D, each bar represents the proportion of all vertical or all lateral movements performed by the head (H), upper torso (U) and lower torso (P). 'Total' refers to the sum of all vertical or all lateral movements performed in 2 h. For the distribution of vertical movements across body parts, only the main effect of Body Part was significant ($F_{2,36} = 77.38$, $P < 0.001$). For lateral movements, the interaction of Group by Body Part was significant ($F_{2,36} = 12.31$, $P < 0.001$). Vertical bars are S.E.M.; every fourth S.E.M. is shown in C. In quinpirole animals, the S.E.M.s of the 5 min intervals ranged from 11 to 27% of the means for vertical movements of the head, from 16 to 51% for vertical movements of the upper torso, and from 44 to 100% for vertical movements of the lower torso. Corresponding values for lateral movements were 1–19%, 7–28%, and 9–35%. For saline rats, the S.E.M.s ranged from 14 to 77% for vertical movements of the head, from 23 to 77% for vertical movements of the lower torso, and from 48 to 100% for vertical movements of the lower torso. Corresponding values for lateral movements were 8–37%, 12–51%, and 17–67%. * and ** indicate $P < 0.05$ and $P < 0.01$, respectively.

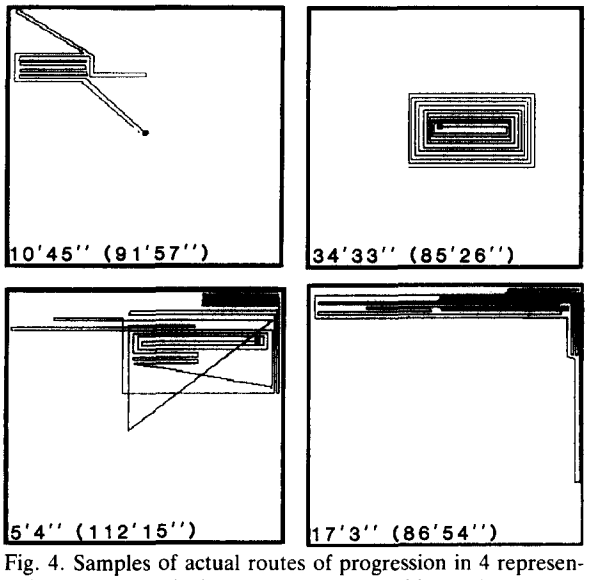


Fig. 4. Samples of actual routes of progression in 4 representative rats injected with quinpirole. To avoid superimposition, repetitions of the same routes are drawn alongside each other. Dots indicate the starting point. The left number in each drawing shows the duration of the sample of progression; the number in brackets is time after injection at which the sample begins.

others, unusually small. The issue of individual variation in responsiveness to quinpirole will be the topic of another publication.

Development of perseveration of routes during the course of drug action

By definition, perseveration is an exaggerated repetition of some aspects of behavior. Since under quinpirole animals travelled repeatedly along a few paths only (Figs. 1 and 2), their progression through the environment appeared perseverative. However, this perseveration was clear only in the second hour of observation when the level of locomotion was high. In the first hour, when the amount of progression was low, repeated travel along the same route was not frequent enough, and therefore, perseveration was not evident. Similarly, perseveration was not evident at any time after injection of saline. In contrast, from about 60 min after quinpirole, repeated travel along the same route could be observed even within relatively short time intervals. This is illustrated for 4 representative animals in Fig. 4. The illustrations indicate that during a sample of time, each animal progressed along the same path repeatedly, with only minor deviations from the route it used before. In summary, perseveration of route induced by quinpirole was present during the second hour of observation, when the amount of locomotion was high, but was not apparent in the first hour, when the amount of locomotion was low.

Movements

Perseveration (stereotypy) of movement also reflects exaggerated repetition of a limited portion of the animal's repertoire. In the present framework, exaggerated frequency of lateral head movements corresponds to stereotyped side-to-side head movements; exaggerated frequency of lateral upper torso movements corresponds to repetitive side-to-side head and foreleg movements. Whereas the exaggerated frequency of movements of the head, or the upper torso, indicate perseveration of movement of a portion of the body, exaggerated frequency of lateral lower torso movements reflects increased frequency of lateral movements of the whole body. The same rules apply also to vertical and forward movements (see Materials and Methods). Consequently, to assess perseveration of movements by a portion of the body, we examine the relative frequencies of head and upper torso movements. These frequencies are analyzed separately for vertical and lateral movements and are compared to the frequencies under saline. To assess perseveration of movement along a single dimension, we examine the relative frequency of total vertical, lateral and forward movements.

As the analysis below indicates, even though quinpirole induced perseveration of routes, it did not induce a perseveration of movements. Animals under quinpirole appeared as free in their movements as normal animals.

Vertical movements. To examine if movements of either the head alone, the upper torso and head together, or lower torso (whole body) dominated vertical movements, the number of times those body parts performed a vertical movement was computed for successive 5 min intervals. Fig. 3 summarizes the results and shows:

(1) Under quinpirole, as under saline, head raising, raising of the upper torso, and rearing on hindquarters, were present throughout the observation period although movements of the lower torso (indicating rearing) were not necessarily present in

every 5 min interval (Fig. 3B). Thus, there was no absence of vertical movements under quinpirole.

(2) Under both quinpirole and saline, 57% of all vertical movements were performed by the head, 40% by the upper torso, and the remainder by the lower torso (Fig. 3D). The similarity between the two groups in the distribution of movements across the body is consistent with the lack of a significant Group by Body Part interaction effect in an analysis of variance performed on the percentage scores ($F_{2,36}$ = 0.02, P = 0.982). Thus, there was no drug-induced domination of vertical movements by a portion of the body.

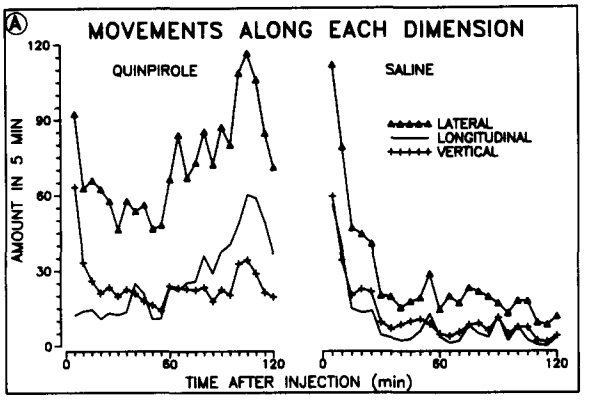
In all, therefore, vertical movements were as free under the drug as under saline.

Lateral movements. As shown in Fig. 3D, quinpirole did not exaggerate lateral movements of the head or of the upper torso. Thus, there was no drug-induced dominaton of lateral movements by a portion of the body. The high relative frequency of lateral movements of the lower torso ($P < 0.001$ compared to either the upper torso or the head) probably indicates movements of the whole body rather than stereotypy. Indeed, during the first few minutes after injection of saline, when the animals are most active, lateral movements of the lower torso prevail as well (Fig. 3C). In all, therefore, lateral movement appeared as free under the drug as under saline.

Forward movements. Although forward movements of the head and upper torso were not quantified, observations of the video tapes indicated that such movements were present in the drug- and saline-treated animals. Both groups exhibited stretching of the torso as well as small forward movements of the head. However, the incidence of forward movements of the whole trunk (recorded as lower torso movement) was elevated. This is evident from the data already presented in Fig. 3A, which showed that forward progression was greater under quinpirole than saline. However, this finding does not indicate perseveration but rather, increased progression of the whole body through the environment. In all, therefore, movement along the forward dimension appeared as free under the drug as under saline.

Distribution of vertical, lateral and forward movements

Perseveration of movement may be produced by the absence of either vertical, lateral, or forward movements. Alternatively, it may be produced by the relative excess of one type of movement. As indicated above, all body parts showed vertical, lateral, and forward movements (Fig. 3), and, therefore, there was no absence of any type of movement. Fig. 5 considers the alternative possibility, namely, whether there is a relative excess of either vertical, lateral or forward movements.



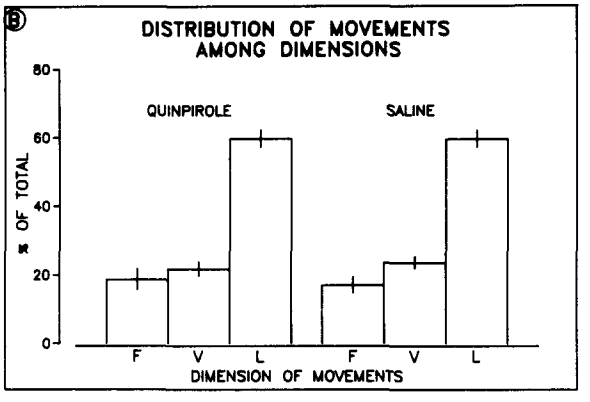


Fig. 5. Time course of the effect of quinpirole on movements along the forward, lateral, and vertical dimensions (A), and the relative distribution of movements across these dimensions (B). For the forward dimension, the amount of movement is the amount of forward progression from Fig. 3A. For the lateral and vertical dimensions, the amount of movement is the sum of all movements performed by body parts along the appropriate dimension (from Fig. 3B,C, respectively). For the calculations of the '% of total', total refers to the sum of forward (F), vertical (V) and lateral (L) movements performed in 2 h. The main effect of Dimension was the only significant effect ($F_{2,36}$ = 116.42, $P < 0.001$). Vertical bars are S.E.M. For quinpirole animals, the S.E.M.s of the 5 min intervals ranged from 24 to 100% of the means for vertical movements, from 7 to 28% for lateral movements, and from 21 to 81% for forward movements. Corresponding values for saline rats were 19–74%, 13–46%, and 8–30%.

Fig. 5A shows a measure of the amount of vertical, lateral and forward movement for rats injected with saline and quinpirole. For vertical and lateral movements, this measure is the sum of, respectively, vertical and lateral movements performed by the 3 body parts; for forward, it is the amount of forward progression (from Fig. 3). To obtain a measure of the relative distribution of movement across the 3 spatial dimensions, the obtained values were assumed as coming from a unidimensional scale, and the percentage of total activity attributed to vertical, lateral, and forward movements computed (Fig. 5B). Inspection of the figure suggests that quinpirole did not exaggerate the relative frequency of movements along any of the dimensions. In both the saline and quinpirole groups, forward movements comprised about 59% of all activity, laterals about 22% and verticals about 17% of all movements. The similarity between the two groups in the distribution of movements across the three dimensions is consistent with the lack of a significant Group by Body Part interaction effect in an analysis of variance performed on the percentage scores ($F_{2,36} = 0.17$, $P = 0.848$). In all, therefore, movement in the three dimensions appeared in similar proportions under the drug as under saline.

Total amount of movements

Although quinpirole did not restrict the freedom of movement, it did elevate the overall amount of movements. Compared to saline, quinpirole significantly increased the total amount of vertical (288.2 ± 65.0 vs 591.7 ± 51.1, $P = 0.002$), lateral (653.5 ± 90.4 vs 1748.3 ± 204.4, $P < 0.001$) and forward (219.9 ± 49.1 vs 652.0 ± 192.1, $P = 0.043$) movements (from Fig. 5). That is, animals under quinpirole were hyperactive.

Specific movements

In addition to inducing perseveration of route and hyperactivity, quinpirole changed the parameters of several types of behavior. Compared to saline, quinpirole reduced the number of animals displaying at least one incidence of face and of body grooming. There was a trend for increased coprophagia and backward locomotion but this missed statistical significance. One of the quinpirole but none of the saline animals showed yawning (Table I). Moreover, although this was not quantified systematically, many drug-treated animals showed one or two brief periods of immobility, usually between 20 and 40 min after injection.

TABLE I

Effect of quinpirole (2 mg/kg) on specific behaviors

Experimental values give no. of animals showing the mentioned behavior. *P*-values refer to results of Fisher's exact probability test.

Behavior	*Saline (n = 10)*	*Quinpirole (n = 10)*	*P*
Face grooming	9	1	0.005
Body grooming	5	0	0.016
Coprophagia	1	6	0.07
Backward locomotion	1	5	0.07
Yawning	0	1	n.s.

DISCUSSION

This study shows that the behavior of rats under quinpirole (2 mg/kg) is characterized by exaggerated repetition of routes, hyperactivity, and absence of perseverative movements. In addition, there is an initial inhibition, and a subsequent excitation of locomotion.

Previous investigators have reported that quinpirole increases locomotion but does not induce stereotyped behavior (e.g. refs. 2, 4). If stereotyped behavior is defined in terms of exaggeration of some types of movements (e.g. side to side head movements) and elimination of others (e.g. rearing), then, based on previous accounts which have been reconfirmed in the present study, it could be concluded that there is no stereotyped behavior under quinpirole. If, however, the definition of stereotyped behavior also includes the repetitive patterning of highly organized forms of behavior (as suggested by Randrup and Munkvad[28]) then our data show that animals under quinpirole are in fact stereotyped because they locomote repeatedly along few routes in a restricted portion of the environment. Thus, administration of this D_2-receptor agonist without the use of concurrent D_1-receptor stimulation, is sufficient to produce stereotyped behavior.

A comparison of the behavioral effects of quin-

pirole observed here to those of amphetamine and apomorphine, suggests that the action of quinpirole resembles most the effects of low doses of amphetamine. While low doses of amphetamine (0.5–1 mg/kg) induce perseveration of route without perseveration of movement, higher doses (2.5–5 mg/kg), induce perseveration of both route and movements[8,11].

Although there is no single study that examined the effects of apomorphine using the distinction between routes and movements, a survey of the literature suggests that perseveration of routes under apomorphine is always accompanied by perseveration of movements. Specifically, a moderate dose (1.25 mg/kg) produces successive elimination of vertical and forward movements, resulting in the perseveration of lateral movements[33,34]. Other studies[18,25] report that the same dose range (1–2 mg/kg), but not lower doses of apomorphine (0.1–0.5 mg/kg), induce perseveration of route. Therefore, perseveration of route without perseveration of movement has been described only under low doses of amphetamine[8,11] and under quinpirole (present study).

The similarity in the profile of perseveration under quinpirole and low doses of amphetamine may reflect a similarity in the mode of action of these substances. We hypothesize that it reflects their action on presynaptic control of dopamine release. The rationale for this hypothesis is as follows. We consider first the action of amphetamine and then of quinpirole.

The dose of amphetamine which produces the shift from perseveration of route to perseveration of route and movements is about 2.5 mg/kg[8,11]. This is the dose at which there is also a qualitative change in the effects of amphetamine on dopamine release. Specifically, below the dose of 2.5 mg/kg, amphetamine's effects on the presynaptic release of dopamine are nerve impulse-dependent but above this dose, they are not[22,35]. Consequently, at the lower doses, although dopamine output is augmented, 'the release of dopamine into the synaptic cleft and the level of interaction between released transmitter and postsynaptic receptor is still regulated by the presynaptic neuron . . .' (ref. 22, p. 47). At the higher doses, however, amphetamine's release of transmitter is no longer regulated, and postsynaptic dopaminergic receptor activity becomes dissociated from presynaptic neuronal firing. According to Kuczenski[22], this dissociation is reflected in the transition from behavioral hyperactivity produced by low doses of amphetamine to 'focused stereotypies' produced by high doses. However, as shown recently[8,11], in addition to hyperactivity, low doses of amphetamine induce perseveration of routes; higher doses induce perseveration of both routes and movements. Consequently, perseveration of route may reflect the enhanced, but regulated presynaptic release of dopamine and perseveration of movements the non-regulated (dissociated) stimulation of postsynaptic dopamine receptors. Accordingly, the balance between these behaviors corresponds to the predominance of regulated vs non-regulated release.

Perseveration of route under quinpirole may reflect similarly a presynaptic action on dopamine release. First, quinpirole stimulates presynaptic receptors regulating release[26,27,37], and presynaptic dopamine receptors are generally more sensitive to agonists than postsynaptic receptors[3,21]. Second, depletion of catecholamines by α-methyl-*p*-tyrosine blocks the behavioral effects of quinpirole[4,6] and of the presynaptic releasing agent, amphetamine[13], suggesting that like amphetamine, quinpirole may act presynaptically. Finally, moderate doses of apomorphine induce perseveration of both movements[34] and routes[18,25], indicating that direct postsynaptic stimulation favors the appearance of perseveration of movements rather than perseveration of routes only.

Thus, like low doses of amphetamine, quinpirole (at the dose used in the present study), may stimulate perseveration of route through presynaptic regulation of dopamine release. However, the drug has other behavioral effects as well: it produes an initial inhibition of locomotion and a subsequent excitation (present study); at lower doses, it induces inhibition only[12] (for a parallel electrophysiological phenomenon, see ref. 21). Therefore, quinpirole acts on probably more than one mechanism.

In light of evidence that quinpirole inhibits dopamine release via stimulation of presynaptic receptors[27], the suggestion that perseveration of route reflects enhanced dopamine release, seems puzzling. Conceivably, quinpirole may be a partial agonist of autoreceptors. As such, it would enhance release, if,

like other forms of stress[1], our test situation (exposure to a novel environment) evokes high dopamine activity. Alternatively, quinpirole may promote release by as yet unknown modes of action.

In summary, like low doses of amphetamine[8,11], quinpirole alters the patterning of routes and does not seem to affect the patterning of movements. This suggests that the organization of routes and the organization of movements are relatively independent and may be controlled by separate neural systems. As such, perseveration of route under quinpirole may be an ideal animal model to investigate the neural basis underlying loss of flexibility in organization of behaviour in space and time.

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REFERENCES

1 Antelman, S.M. and Chiodo, L.A., Amphetamine as a stressor. In I. Creese (Ed.), *Stimulants: Neurochemical, Behavioral, and Clinical Perspectives,* Raven, New York, 1983, pp. 269–299.
2 Arnt, J., Hyttel, J. and Perregaard, J., Dopamine D-1 receptor agonists combined with the selective D-2 agonist quinpirole facilitate the expression of oral stereotyped behaviour in rats, *Eur. J. Pharmacol.,* 133 (1987) 137–145.
3 Bannon, M.J. and Roth, R.H., Pharmacology of mesocortical dopamine neurons, *Pharmacol. Rev.,* 35 (1983) 53–68.
4 Barone, P., Davis, T.A., Braun, A.R. and Chase, T.N., Dopaminergic mechanisms and motor function: characterization of D-1 and D-2 dopamine receptor interactions, *Eur. J. Pharmacol.,* 123 (1986) 109–114.
5 Beck, C.H.M., Chow, H.L. and Cooper, S.J., Dose-related response of male rats to apomorphine — snout contact in the open-field, *Physiol. Behav.,* 37 (1986) 819–825.
6 Braun, A.R. and Chase, T.N., Obligatory D-1/D-2 receptor interaction in the generation of dopamine agonist related behaviors, *Eur. J. Pharmacol.,* 131 (1986) 301–306.
7 Creese, I., Sibley, D.R., Hamblin, M.W. and Leff, S.E., The classification of dopamine receptors: relationship to radioligand binding, *Annu. Rev. Neurosci.,* 6 (1983) 43–71.
8 Eilam, D., *Exploratory Behavior in Norway Rats (Rattus norvegicus): Normal Behavior and the Behavior under the Psychoactive Drug Amphetamine,* Doctoral dissertation, Tel-Aviv University, Ramat Aviv, Israel, 1987.
9 Eilam, D. and Golani, I., The ontogeny of exploratory behavior in the house rat (*Rattus rattus*): the mobility gradient, *Dev. Psychobiol.,* 21 (1988) 679–710.
10 Eilam, D. and Golani, I., Home base behavior of rats (*Rattus norvegicus*) exploring a novel environment, *Behav. Brain Res.,* in press.
11 Eilam, D. and Golani, I., Excursions from home base are amalgamated, in exploratory behavior of rats under amphetamine, into stereotyped routes, *Behav. Brain Res.,* submitted.
12 Eilam, D. and Szechtman, H., D-2 agonist quinpirole induces inhibition and excitation of forward progression, *Soc. Neurosci. Abstr.,* 14 (1988) 1076.
13 Ernst, A.M., Mode of action of apomorphine and dexamphetamine on gnawing compulsion in rats, *Psychopharmacology,* 10 (1967) 316–323.
14 Eshkol, N., *50 Lessons by Dr. M. Feldenkrais,* The Movement Notation Soc., Holon, Israel, 1980, 160 pp.
15 Eshkol, N. and Wachmann, A., *Movement Notation,* Weidenfeld and Nicolson, London, 1958.
16 Flicker, C. and Geyer, M.A., Behavior during hippocampal microinfusions. I. Norepinephrine and diversive exploration, *Brain Res. Rev.,* 44 (1982) 79–103.
17 Geyer, M.A., Russi, P.V. and Masten, V.L., Multivariate assessment of locomotor behavior: pharmacological and behavioral analyses, *Pharmacol. Biochem. Behav.,* 25 (1986) 277–288.
18 Geyer, M.A., Russi, P.V., Segal, D.S. and Kuczenski, R., Effects of apomorphine and amphetamine on patterns of locomotor and investigatory behavior in rats, *Pharmacol. Biochem. Behav.,* 28 (1987) 393–399.
19 Golani, I., Homeostatic motor processes in mammalian interaction: a choreography of display. In P.P.G. Bateson and P.H. Klopfer (Eds.), *Perspectives in Ethology,* Plenum, New York, 1976, pp. 69–134.
20 Golani, I., Wolgin, D. and Teitelbaum, P., A proposed natural geometry of recovery from akinesia in the lateral hypothalamic rat, *Brain Research,* 164 (1979) 237–267.
21 Hu, X.-T. and Wang, R.Y., Disinhibition of nucleus accumbens neurons by the dopamine D_2 receptor agonist LY-141865: prevented by 6-OHDA pretreatment, *Brain Research,* 444 (1988) 389–393.
22 Kuczenski, R., Biochemical actions of amphetamine and other stimulants. In I. Creese (Ed.), *Stimulants: Neurochemical, Behavioral, and Clinical Perspectives,* Raven, New York, 1983, pp. 31–61.
23 Mashurano, M. and Waddington, J.L., Stereotyped behaviour in response to the selective D-2 dopamine receptor agonist RU 24213 is enhanced by pretreatment with the selective D-1 agonist SK&F 38393, *Neuropharmacology,* 25 (1986) 947–949.
24 Moore, N.A. and Axton, M.S., Production of climbing behaviour in mice requires both D1 and D2 receptor activation, *Psychopharmacology,* 94 (1988) 263–266.
25 Pisa, M. and Szechtman, H., Lateralized and compulsive exteroceptive orientation in rats treated with apomorphine, *Neurosci. Lett.,* 64 (1986) 41–46.
26 Plantje, J.F., Dijcks, F.A., Verheijden, P.F.H.M. and Stoof, J.C., Stimulation of D-2 dopamine receptors in rat

mesocortical areas inhibits the release of [^{3}H]dopamine, *Eur. J. Pharmacol.*, 114 (1985) 401–402.
27 Plantje, J.F., Steinbusch, H.W.M., Schipper, J., Dijcks, F.A., Verheijden, P.F.H.M. and Stoof, J.C., D-2 dopamine-receptors regulate the release of [^{3}H]dopamine in rat cortical regions showing dopamine immunoreactive fibers, *Neuroscience*, 20 (1987) 157–168.
28 Randrup, A. and Munkvad, I., Stereotyped activities produced by amphetamine in several animal species and man, *Psychopharmacology (Berlin)*, 11 (1967) 300–310.
29 Robertson, G.S. and Robertson, H.A., Synergistic effects of D1 and D2 dopamine agonists on turning behaviour in rats, *Brain Research*, 384 (1986) 387–390.
30 Robertson, G.S. and Robertson, H.A., D1 and D2 dopamine agonist synergism: separate sites of action?, *Trends Pharmacol. Sci.*, 8 (1987) 295–299.
31 Schiorring, E., An open field study of stereotyped locomotor activity in amphetamine-treated rats, *Psychopharmacology*, 66 (1979) 281–287.
32 Seeman, P., Brain dopamine receptors, *Pharmacol. Rev.*, 32 (1980) 229–313.
33 Szechtman, H., Ornstein, K., Hofstein, R., Teitelbaum, P. and Golani, I., Apomorphine induces behavioral regression: a sequence that is the opposite of neurological recovery. In E. Usdin, T.L. Sourkes and M.B.H. Youdim (Eds.), *Enzymes and Neurotransmitters in Mental Disease*, Wiley, Chichester, 1980, pp. 511–517.
34 Szechtman, H., Teitelbaum, P., Ornstein, K. and Golani, I., The morphogenesis of stereotyped behavior induced by the dopamine receptor agonist apomorphine in the laboratory rat, *Neuroscience*, 14 (1985) 783–798.
35 Von Voigtlander, P.F. and Moore, K.E., Involvement of nigro-striatal neurons in the in vivo release of dopamine by amphetamine, amantadine and tyramine, *J. Pharmacol. Exp. Ther.*, 184 (1973) 542–552.
36 Walters, R.J., Bergstrom, D.A., Carlson, J.H., Chase, T.N. and Braun, A.R., D1 dopamine receptor activation required for postsynaptic expression of D2 agonist effects, *Science*, 236 (1987) 719–722.
37 Zetterström, T., Sharp, T. and Ungerstedt, U., Effect of dopamine D-1 and D-2 receptor selective drugs on dopamine release and metabolism in rat striatum in vivo, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 334 (1986) 117–124.