*Pharmacology Biochemistry and Behavior*, Vol. 44, pp. 627–632, 1993
Printed in the U.S.A. 

0091-3057/93 $6.00 + .00


# Behavioral Sensitization and Tolerance to the $D_2$ Agonist RU 24213: Dissociation Between Several Behavior Patterns in Mice

EZIO TIRELLI[1] AND CHRISTINE JODOGNE

*Laboratoire de Psychologie Expérimentale, Université de Liége au Sart-Tilman, boulevard du rectorat 5, Bt. 32, B-4000, Liége-1, Belgium*

Received 20 April 1992

TIRELLI, E. AND C. JODOGNE. *Behavioral sensitization and tolerance to the $D_2$ agonist RU 24213: Dissociation between several behavior patterns in mice.* PHARMACOL BIOCHEM BEHAV **44**(3) 627–632, 1993.—Previous studies have shown that different components of behavioral effects of indirect agonists given chronically to laboratory rodents can follow different courses during treatment. Whether repeated injections of a $D_2$ agonist can lead to the same phenomenon was investigated in mice using the $D_2$ agonist *N*-*n*-propyl-*N*-phenylethyl-*p*-(3-hydroxy-phenyl)-ethylamine (RU 24213). Five mutually exclusive behaviors were examined over seven intermittent administrations (every other day over 13 daily injections) of RU 24213 (2.5 mg/kg SC) in mice. Rapid tolerance to the clearest initial effect of RU 24213, stillness, was found. Suppression of grooming also showed tolerance later in the treatment regimen (from the fourth test). From the third test, parallel time courses of sensitization were obtained for ambulation and rearing. Sleeping position was strongly depressed throughout the chronic treatment. These results show that the development in time of the behavioral effects of RU 24213 injected chronically strongly depend upon the behavioral measure. This supports the use of multiple measures in the same animal in the behavioral analysis of chronically injected dopaminergic drugs.

RU 24213 $D_2$ receptors Sensitization Tolerance Motor depression Ambulation Rearing Grooming Mice

UNDER certain circumstances, intermittent administration of postsynaptic dopamine $D_2$ receptor agonists can lead to the emergence and increment of specific behaviors in laboratory rodents. These include, for example, increases in forward walking and rearing in rats injected daily or every other day with quinpirole or (+)-4-propyl-9-hydroxynaphthoxazine (PHNO) and exposed repeatedly to the same test context (6,7,16,17,19,36). Also, rats with unilateral lesions of the nigrostriatal pathway show sensitization to the contraversive circling induced by intermittently injected bromocriptine, another $D_2$ agonist (31). No licking, gnawing, or mouthing behaviors emerged in these experiments, as is often the case with amphetamine-like drugs and other psychomotor stimulants administered chronically [for a review, see (28)]. Some of the behavioral effects of the mixed $D_2/D_1$ agonist apomorphine (intense ambulation in rats, gnawing and climbing in mice, and aggressive behaviors in both species) can develop sensitization and cross-sensitization either during a repeated-injection regimen or after chronic treatment with a postsynaptic dopamine agonist given in the home cages (2,4,8, 18,27,32,39). There are also a few studies showing tolerance to the effects of postsynaptic dopamine agonists, in particular to hypokinesia induced by apomorphine, piribedil, and bromocriptine (3,32). Whether or not a given chronic treatment will lead to tolerance or sensitization, or to no change, depends upon whether administration is intermittent or continuous. Strong determinants include factors like interinjection interval, light-dark cycle, and the relative quietness of the testing room (2,16,17,18,28). Nevertheless, it is possible to obtain sensitization and cross-sensitization to behavioral effects of $D_2$ agonists during or after continuous administration (via osmotic pumps or stomachic infusion) in rats and mice (14,16,17,38,40,41). Another critical factor is the behavior pattern measured. Reports have described, in cats, rats, and mice chronically treated with amphetamine, cocaine, or fencamfamine, different rates and time courses (increment, decrement, or no change) of distinct behavioral components of the stimulant effects of these drugs (1,5,25,26,30).

In contrast to the large number of studies with chronic psychomotor stimulants, or with dopamine antagonists, little is known about the behavioral changes that occur during chronic administration of selective postsynaptic dopamine $D_2$

[1] To whom requests for reprints should be addressed.

agonists [for short reviews, see (9,28)]. Therefore, in this study we investigated the behavioral effects induced by the $D_2$ agonist *N*-*n*-propyl-*N*-phenylethyl-*p*-(3-hydroxy-phenyl)-ethylamine (RU 24213) chronically injected in mice, a compound for which no data concerning chronic behavioral effects are available as yet. Our main question was whether intermittent treatment of a $D_2$ agonist can produce differential effects according to behavioral components. A number of behavior patterns were included in this study: stillness (standing still), grooming, sleeping posture, ambulation, and rearing (including leaning on the wall). This behavioral categorization was devised such that the behaviors measured were mutually exclusive, so facilitating the identification of possible dissociative changes. Note that sniffing, a behavior often examined in psychopharmacological studies of the dopamine system, was not included because it is often combined with other ongoing behaviors such as ambulation, rearing, or standing still.

TABLE 1

CATEGORIES OF BEHAVIOR PATTERNS ASSESSED

| | |
|---|---|
| Stillness | Stationary, sitting posture, and opened eyes, with or without sniffing. |
| Grooming | Face and body washing strokes with the forepaws, scratching with hindlimbs, anogenital licking, tail nibbling |
| Sleeping | Sleeping posture, curled or nearly curled body while lying still and closed eyes |
| Ambulation | Horizontal displacement of the body in the space; forward walking, with or without sniffing |
| Rearing | Body in a vertical or near-vertical plane with or without front paws against the wall, and with or without sniffing |

## METHOD

### *Animals*

Fifty-six male outbred OF-1 mice (40 in Experiment 1 and 16 in Experiment 2) weighing 30–35 g born in our laboratory colony (from a stock purchased from IFFA-CREDO, Oncins, France) were used. Mice were housed in groups of eight in plastic cages with pine sawdust bedding and free access to food (standard chow pellets) and tapwater. Room temperature was maintained at 22–24°C and humidity uncontrolled. Lighting was on a 12 L : 12 D cycle with lights on at 0800 h. Mice were used only once.

### *Apparatus*

In both experiments, mice were observed in eight individual, adjacent chambers (clear acrylic, 27 × 14 × 30 cm). The acrylic floors were subdivided by yellow lines into three equal areas (9 × 14 cm). All experiments were carried out during the light phase of the light cycle, 1230–1700 h, in a diffusely illuminated room maintained at 22–25°C.

### *Procedure*

RU 24213 was dissolved in saline (0.9% NaCl) and prepared immediately before each injection. Mice received a constant volume of drug (or saline for the controls) to 0.01 ml/g body weight. In Experiment 1, mice were injected with saline, 2.5, 5, 10, or 20 mg/kg RU 24213) SC and immediately placed into the experimental chambers. In Experiment 2, for 13 daily sessions mice were injected with either 2.5 mg/kg RU 24213 or saline SC and placed into the testing chambers. Test observations were made every other day, beginning with the first injection (day one). Behavioral observations began 10 min after injection using a mixed multiple-subject time-sampling procedure (35). Each mouse was observed in the 11th, 21st, 31st, and 41st min (after injection). Each animal was thus observed four times, separated by 9 min; hence, the total individual duration of behavioral observation during the 40-min session was 1 min × 4 = 4 min. During the 9-min intervals between observations of a given mouse, the other mice (7) were observed each in turn. The remaining minute of each observational series served as a pause for the observer. The tests were organized into two sessions per day, with four mice from each treatment (drug or saline) in each session. Behavioral categories (described in Table 1) included the most frequently observed behavior patterns in our experimental conditions: stillness, grooming (all patterns), sleeping position, ambulation, and rearing. Given that elicitation of licking and gnawing is a possible effect of dopamine agonists, two other categories were also included for recording these two oral behaviors. Rearing bouts were simply counted over the four 1-min observational samples. Ambulation was scored as the number of times a mouse crossed from one of the three floor areas to another. Stillness, grooming, and sleeping position were evaluated using a point-sampling schedule inserted into the 1-min samples. Within each sample, an instantaneous check was made every 5 s and the behavior exhibited at that instant (grooming, standing still, or sleeping) was recorded. There was thus a maximum of 12 checks per 1-min period and the highest possible number of occurrences for one behavior was 12 × 4 = 48. The observer was unaware of the pharmacological treatment during observation.

### *Data Analyses*

Data from Experiment 1 were analysed using *a priori* Dunnett's tests that provided, without the requirement of a one-way analysis of variance (ANOVA), determination of differences between the individual means and the control mean (13). Data from Experiment 2 were analyzed using a mixed two-way ANOVA on each behavior, where drug and day of testing were taken as a between-subject factor (two levels) and a within-subject factor (seven levels), respectively. To adjust for potential violations of the assumptions of compound symmetry and sphericity, the Greenhouse–Geisser correction was also computed. Nevertheless, because all significant effects reported here remained robustly significant after correction for clarity the original degrees of freedom are given in the text. Differences between means were assessed with a posteriori Tukey's honest significant differences (HSD) tests, derived from the appropriate error mean squares given by significant day × drug interactions (13). Statistical significance was established at a $p$ level of 0.05.

## RESULTS

### *Experiment 1*

As can be seen in Fig. 1, all doses of RU 24213 produced stillness, but there was no dose dependence (no significant differences between doses means). Interestingly, mice never

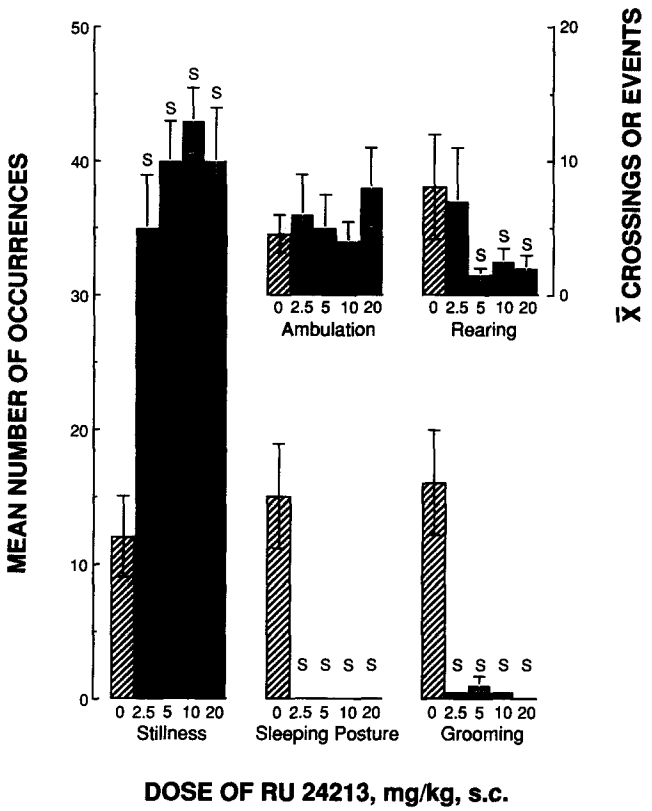


FIG. 1. Effects of the $D_2$ agonist *N*-*n*-propyl-*N*-phenylethyl-*p*-(3-hydroxy-phenyl)-ethylamine (RU 24213) on different individual behaviors in mice. Injections were given SC 10 min before visual observation (time-sampling technique). Note that the maximal possible score was 48. Vertical brackets indicate SE. (S), significantly different as compared to the control mean (0 mg/kg), taken at a $p$ level of 0.01 (*a priori* Dunnett's tests).

displayed any adoption of sleeping posture at all, suggesting that the stillness induced by the $D_2$ agonist is not related to sleeping. Note that control mice always adopted sleeping position during the second part of the session (not shown). Correlating with the predominant stillness induced by RU 24213, grooming was almost abolished at all doses. RU 24213 did not alter ambulation, even at a relatively high dose (20 mg/kg); on the other hand, rearing was strongly diminished at the three higher doses (5, 10, and 20 mg/kg) but not at all after 2.5 mg/kg RU 24213. All these effects were significant by *a priori* Dunnett's tests ($p < 0.01$). It is important to note that no oral behaviors (licking, gnawing, or other orofacial movement) were detected.

*Experiment 2*

Figure 2 shows separate profiles for stillness, grooming, sleeping position, ambulation, and rearing. The decline in stillness in the RU 24213-injected group contrasts with the absence of changes over testing days in controls. This decline was rapid because the amount of stillness seen after three injections (second test day) was significantly lower than that seen on the first test day. After five injections (third testing day), levels were half those on the first test. However, mice receiving RU 24213 showed significant stillness after 13 injections (seventh test). This profile was supported by a significant interaction between drug and day of testing, $F(6, 84) = 14.98$, $p < 0.0001$, and by *a posteriori* Tukey's HSD tests.

In conjunction with the decrease in stillness scores, ambulation and rearing increased over the chronic treatment, reaching a plateau between the 9th and 13th days of treatment. This increase was significant from test day 3 (after five injections). These similar profiles were statistically supported by significant drug × day interactions, $F(6, 84) = 3.48$, $p < 0.0041$; $F(6, 84) = 3.03$, $p < 0.0098$, respectively.

Grooming, which was suppressed by RU 24213 after the first injection (first day), increased abruptly by test day 4, whereas control mice did not show any change in this behavior over the chronic treatment. Grooming levels of RU 24213-treated mice almost reached control levels on test day 5 (ninth injection). A significant drug × day interaction supported these changes, $F(6, 84) = 2.93$, $p < 0.0121$.

In contrast with the other behaviors under study, the amount of time spent in a sleeping position, virtually suppressed by RU 24213, did not change over the chronic treatment. Control mice showed some variability in sleeping posture from one test day to another, the last test yielding higher, but nonsignificant, levels of sleeping (when compared to the mean of the first test day). This pattern was supported by a significant main effect of drug, $F(1, 14) = 33.53$, $p < 0.0001$, with no evidence for an interaction ($F < 1$).

## DISCUSSION

In Experiment 1, mice receiving acute injection of RU 24213 showed considerable stillness and little sleeping position, grooming, and rearing. Ambulation, even at large doses (such as 10 or 20 mg/kg), did not seem altered by the dopamine agonist. These results reflect one of the most consistent effects reported for $D_2$ agonists in mice and rats: general motor depression (10,11,12,15,20,22,29,33,34,37). But, when looked at in detail our results differ from those reported by, for example, Starr and Starr (33,34) and Waddington and colleagues (20,29), who injected RU 24213 in mice and rats, respectively. In these studies, RU 24213 at 15–20 mg/kg induced intense ambulation coupled with sniffing directed toward the floor and stillness with reduced ambulation at several smaller doses. Nevertheless, our data fully agree with those of Mueller and colleagues (22), who used rats. The absence of impact of RU 24213 on ambulation in our mice might be due to a lack of sensitivity in the measurement scale. Also relevant in these discrepancies are species, strain, duration of observation, and the differing accuracies with which the behavior patterns were described.

In Experiment 2, we found that rapid augmentation of ambulation and rearing to unusually high levels was preceded and accompanied by a recovery of normal, or near normal, levels of stillness and grooming. The former event resembles sensitization while the second resembles tolerance. A similar continuous tolerance to the hypokinetic action (depression of wheel running) of the dopamine $D_2$ agonist bromocriptine injected six times every other day has been reported previously in mice (32). Zhou and colleagues (41) found that the continuous administration of the $D_2$ agonist quinpirole to mice (via osmotic implants) produced an augmentation followed by a clear diminution of irritability and growing hyperlocomotion (almost absent at the beginning).

It seems difficult to attribute, by virtue of the principle of mutual exclusion, the increment of ambulation and rearing to

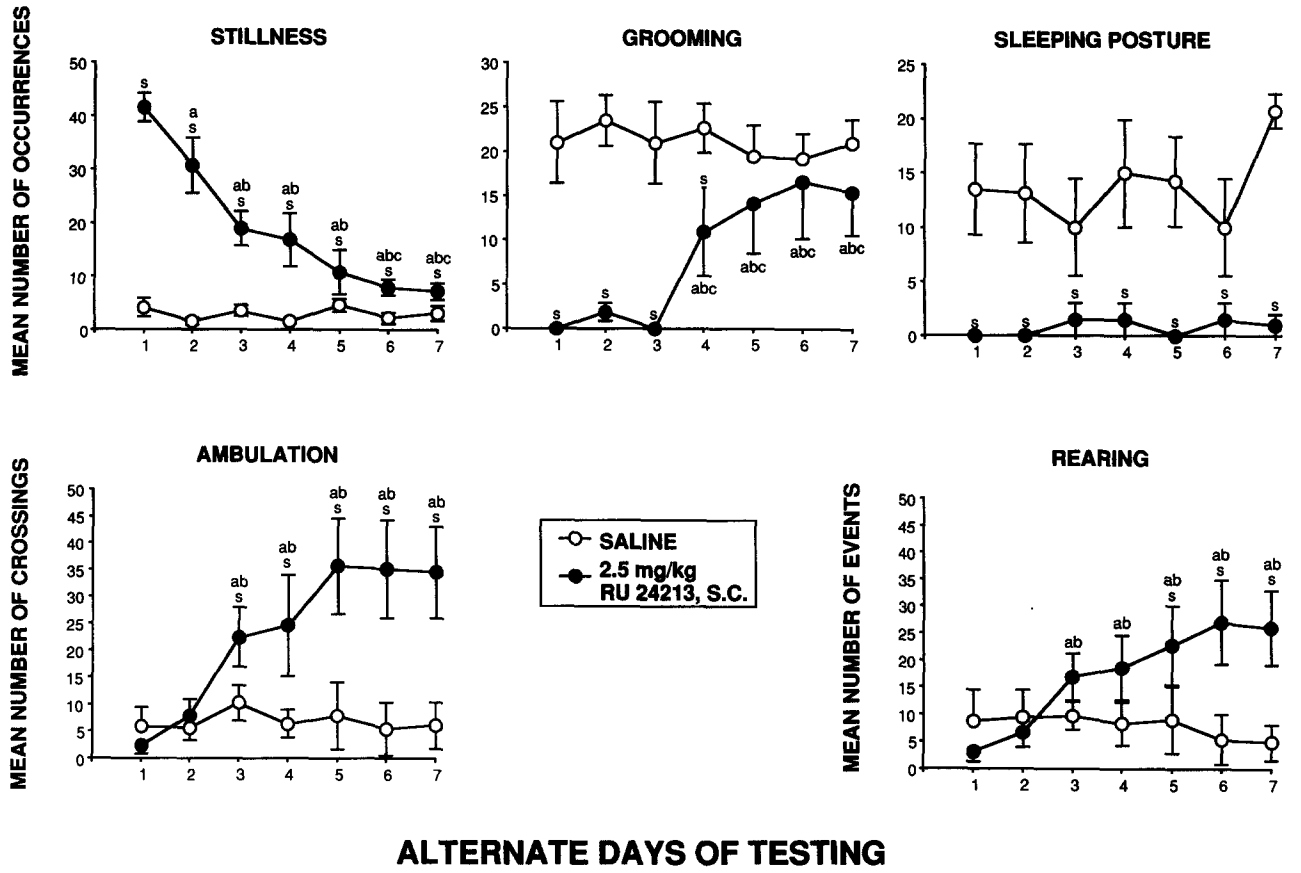


FIG. 2. Effects of daily administered *N*-*n*-propyl-*N*-phenylethyl-*p*-(3-hydroxy-phenyl)-ethylamine (RU 24213) on five behaviors in mice. Injections were given SC for 13 days. Mice were placed singly into the experimental chambers after each injection but tested every other day. The first day of testing took place after the first injection. The maximal possible score was 48. Vertical brackets indicate SE. (S), significantly different as compared to the other mean of the same test day; (a), significantly different from the initial mean (first test day) receiving the same treatment; (b), from the second mean (second test day); (c) from the third mean (third test day); all taken at a $p$ level of 0.05 after Tukey's honest significant differences tests and a mixed two-way analysis of variance.

the decrement of stillness. Rather, the converse relationship is more likely, stillness disappearing progressively with the emergence of the stimulant effects of RU 24213. Interestingly, during the fourth test day grooming reached a level significantly higher than the initial levels and lower than the control level. The fact that the levels of the four other behaviors did not change substantially as compared to the preceding test day (third test, where grooming was completely suppressed) suggests that the increment of grooming on the fourth test day was not due to changes in some other behaviors. This means that grooming may have undergone tolerance. The relative independence of grooming from the other behaviors is also sustained by the fact that there were sharp differences between the levels at the three first tests for stillness, ambulation, and rearing, whereas grooming was suppressed almost equally over the three first tests. Finally, on tests 5, 6, and 7 a stabilization of the effects of RU 24213 took place for all behavior patterns. The fact that grooming levels did not supercede normal levels may reasonably be attributed to the high rates of ambulation and rearing impeding the full expression of grooming. The constant suppression of sleeping posture over the 13-day treatment might also be indicative, at least in part, of an increase of wakefulness. This would be consistent with studies describing a decrease of rapid eye movement (REM) sleep in rats and rabbits after injection of $D_2$ agonists (21,23,24). Another possibility, perhaps more likely, is that the prevalence of the other behaviors did not allow for sleeping position to be exhibited before the end of the testing session.

Our data complement previous work showing that behavioral tolerance and sensitization should not be considered as a unitary, one-dimensional, phenomenon, that is, different components of the behavioral changes induced by dopamine agonists injected intermittently repeatedly show differential development. Thus, for example, Castellani and colleagues (1) reported that repeated injections of cocaine in cats led to a tolerance to "preseizure" patterns (e.g., hypertonia and forelimbs splaying) combined with a sensitization to dystonic posturing. Likewise, sensitization to sniffing induced by amphetamine or fencamfamine is reportedly accompanied by tolerance to licking or rearing in rats [(5,26), respectively]. Yet, during intermittent injections of methamphetamine in mice a slow increment in locomotor behaviors can develop collaterally to a rapid increase, plateau, and decrease of oral behaviors (25).

In conclusion, the results indicate that, depending upon

the behavior pattern, the same animal can develop tolerance, sensitization, and absence of behavioral changes during intermittent administration with a postsynaptic dopamine agonist. Thus, the behavioral changes that occur during such treatment are not unitary. This should be taken into account in selecting behavioral responses for measurement during chronic experiments using dopamine agonists.

ACKNOWLEDGEMENTS

The authors thank ROUSSEL UCLAF, Romainville, France, for the generous gift of RU 24213 and Philip Terry for critical reading of the manuscript. Christine Jodogne was, during the realization of the present study, under contract with the Fonds National de la Recherche Scientifique (F.N.R.S., Brussels, Belgium) as a Research Assistant.

## REFERENCES

1. Castellani, S.; Ellinwood, E. H.; Kilbey, M. M. Behavioral analysis of chronic cocaine intoxication in the cat. Biol. Psychiatry 13: 203-215; 1978.
2. Castro, R.; Abreu, P.; Calzadilla, C. H.; Rodriguez, M. Increased or decreased locomotor response in rats following repeated administration of apomorphine depends on dosage interval. Psychopharmacology (Berl.) 85:333-339; 1985.
3. Costentin, J.; Marcais, H.; Protais, P.; Schwartz, J.-C. Tolerance to hypokinesia elicited by dopamine agonists in mice: Hyposensitization of receptors? Life Sci. 20:883-886; 1977.
4. Duterte-Boucher, D.; Costentin, J. Appearance of a stereotyped apomorphine-induced climbing in unresponsive DBA/2 mice after subchronic manipulations of brain dopamine transmission. Psychopharmacology (Berl.) 98:56-60; 1989.
5. Eichler, A. J.; Antelman, S. M.; Black, C. A. Amphetamine stereotypy is not a homogeneous phenomenon: Sniffing and licking show distinct profiles of sensitization and tolerance. Psychopharmacology (Berl.) 68:287-290; 1980.
6. Eilam, D.; Canaran, G.; Szechtman, H. Compulsive and rigid locomotion produced by chronic treatment with the D2 agonist quinpirole. Soc. Neurosci. Abstr. 15:460.9; 1989.
7. Eilam, D.; Szechtman, H. Dosing regimen differentiates sensitization of locomotion and mouthing to D2 agonist quinpirole. Pharmacol. Biochem. Behav. 36:989-991; 1990.
8. Gotsick, J. E.; Drew, W. G.; Proctor, D. L. Apomorphine-induced aggression: An evaluation of possible sensitizing factors in the rat. Pharmacology 13:385-390; 1975.
9. Greenshaw, A. J.; Baker, G. B.; Wishart, T. B. Dopamine receptor changes during chronic drug administration. In: Goudie, A. J.; Emmett-Oglesby, M. W., eds. Psychoactive drugs: Tolerance and sensitization. Clifton, NJ: Humana Press; 1989.
10. Jackson, B. M.; Martin, L. P.; Larsson, L.-G.; Cox, R. F.; Wasczak, B. L.; Ross, S. B. Behavioral, biochemical and electrophysiological studies on the motor depressant and stimulant effects of bromocriptine. Naunyn Schmiedebergs Arch. Pharmacol. 342: 290-299; 1989.
11. Jackson, D. M.; Ross, S. B.; Edwards, S. R. Dopamine D2 agonist-induced behavioral depression is reversed by dopamine D1 agonists. J. Neural Trans. 75:213-220; 1989.
12. Jackson, D. M.; Ross, S. B.; Larsson, L. G.; Dopamine D-2 receptor agonist-induced behavioral depression: Critical dependence upon postsynaptic dopamine D-1 function. Naunyn Schmiedebergs Arch. Pharmacol. 340:355-365; 1990.
13. Kirk, R. E. Experimental design: Procedures for the behavioral sciences. 2nd ed. Monterey, CA: Brooks/Cole; 1982.
14. Le, W.-D.; Zhou, X.-D.; Guo-Zhang, J. Enhanced stereotypic behavior by chronic treatment with bromocriptine accompanies increase of D1 receptor binding. Life Sci. 42:1841-1845; 1988.
15. Martin, G. E.; Bendesky, R. J. Mouse locomotor activity: An in vivo test for dopamine autoreceptor activation. J. Exp. Pharmacol. Ther. 229:706-711; 1984.
16. Martin-Iverson, M. T.; Iversen, S. D.; Stahl, S. M. Long-term motor stimulant effects of (+)-4-propyl-9-hydroxynaphthoxazine (PHNO), a dopamine D-2 receptor agonist: Interactions with a dopamine D-1 receptor antagonist and agonist. Eur. J. Pharmacol. 149:25-31; 1988.
17. Martin-Iverson, M. T.; Stahl, S. M.; Iversen, S. D. Chronic administration of a selective dopamine D-2 agonist: Factors determining behavioral tolerance and sensitization. Psychopharmacology (Berl.) 95:534-539; 1988.
18. Mattingly, B. A.; Gotsick, J. E.; Salamanca, K. Latent sensitization to apomorphine following repeated low doses. Behav. Neurosci. 102:553-558; 1988.
19. Mazurski, E. J.; Beninger, R. J. The dopamine D-2 agonist quinpirole produces environment-specific conditioned activity. Pharmacol. Biochem. Behav. 30:525-527; 1988.
20. Molloy, A. G.; Waddington, J. L. The enantiomers of SKF 83566, a new selective D1 dopamine antagonist, stereospecifically block stereotyped behaviour induced by apomorphine and by the selective D2 agonist RU 24213. Eur. J. Pharmacol. 116:183-186; 1985.
21. Monti, J. M.; Hawkins, M.; Jantos, H.; D'Angelo, L.; Fernandez, M. Biphasic effects of dopamine D-2 receptor agonists on sleep and wakefulness in the rat. Psychopharmacology (Berl.) 95: 395-400; 1988.
22. Mueller, E.; Bordi, F.; Bohmaker, K. Enhancement by the D1 dopamine agonist SKF 38393 of specific components of stereotypy elicited by the D2 agonists LY 171555 and RU 24213. Life Sci. 42:2561-2657; 1988.
23. Ongini, E.; Caporali, M. G. Differential effects of dopamine D-1 and D-2 receptor agonists on EEG activity and behaviours in the rabbit. Neuropharmacology 26:355-360; 1987.
24. Ongini, E.; Longo, V. G. Dopamine receptor subtypes and arousal. Int. Rev. Neurobiol. 31:239-255; 1989.
25. Peachey, J. E.; Rogers, B.; Brien, J. F.; Maclean, A.; Rogers, D. Measurement of acute and chronic behavioural effects of methamphetamine in the mouse. Psychopharmacology (Berl.) 48: 271-275; 1976.
26. Planeta, C. S.; Scavone, C.; De Lucia, R.; Aizenstein, M. L. Behavioural effects of long-term administration of fencamfamine: Neurochemical implications. Gen. Pharmacol. 18:347-349; 1987.
27. Porreca, F.; Cowan, A.; Tallarida, J. Differentiation of apomorphine from bromocriptine, piribedil and TRH by chronic administration in rats. Psychopharmacology (Berl.) 76:70-74; 1982.
28. Post, R. M. Central stimulants: Clinical and experimental evidence on tolerance and sensitization. In: Israel, Y.; Glaser, F. B.; Kalant, H.; Popham, R. E.; Schmidt, W.; Smart, R. G., eds. Research advances in alcohol and drug problems. vol. 6. New York: Plenum Press; 1981:1-65.
29. Pugh, M. T.; O'Boyle, K. M.; Molloy, A. G.; Waddington, J. L. Effects of the putative D1 antagonist SCH 23390 on stereotyped behaviour induced by the D2 agonist RU 24213. Psychopharmacology (Berl.) 87:308-312; 1985.
30. Rebec, V. G.; Segal, D. S. Apparent tolerance to some aspects of amphetamine stereotypy with long-term treatment. Pharmacol. Biochem. Behav. 13:793-797; 1980.
31. Rouillard, C.; Bedard, P. J.; Falardeau, P.; Di Paolo, T. Behavioral and biochemical evidence for a different effect of repeated administration of L-DOPA and bromocriptine on denervated versus non-denervated striatal dopamine receptors. Neuropharmacology 26:1601-1606; 1987.
32. Smith, R. C.; Strong, J. R.; Hicks, P. B.; Samorajski, T. Behavioral evidence for supersensitivity after chronic bromocriptine administration. Psychopharmacology (Berl.) 60:241-246; 1979.
33. Starr, B. S.; Starr, M. S. Differential effects of dopamine D1 and D2 agonists and antagonists on velocity of movement, rearing

and grooming in the mouse: Implications for the roles of D1 and D2 receptors. Neuropharmacology 25:455–463; 1986.
34. Starr, B. S.; Starr, M. S. Behavioural interactions involving D1 and D2 dopamine receptors in nonhabituated mice. Neuropharmacology 26:613–619; 1987.
35. Suen, H. K.; Ary, D. Analysing quantitative behavioral observation data. Hillsdale, NJ: Lawrence Erlbaum; 1989.
36. Szechtman, H.; Canaran, G.; Ibrahim, F.; Eilam, D. Nonlinear sensitization of sensitivity produced by chronic treatment with D2 agonist quinpirole. Soc. Neurosci. Abstr. 15:460.8; 1989.
37. Waddington, J. L.; O'Boyle, K. M. Drugs acting on brain dopamine receptors: A conceptual reevaluation five years after the first selective D1 antagonist. Pharmacol. Ther. 43:1–52; 1989.
38. Weiss, B.; Zhou, L.-W.; Chen, J. F.; Seele, F.; Bai, G. Distribution and modulation of the D2 dopamine receptor mRNA in mouse brain: Molecular and behavioral correlates. Adv. Biosci. 77:9–26; 1988.
39. Wilcox, R. E.; Riffe, W. H.; Chen, P.-C.; Hammett, S.; Smith, R. V. Behavioral facilitation following chronic administration of *N-n*-propylnorapomorphine. Psychopharmacology (Berl.) 72: 113–115; 1980.
40. Winkler, J. D.; Weiss, B. Effect of continuous exposure to selective D1 and D2 dopaminergic agonists on rotational behavior in supersensitive mice. J. Exp. Pharmacol. Ther. 249:507–516; 1989.
41. Zhou, L.-W.; Qin, Z.-H.; Weiss, B. Downregulation of stereotyped behavior and production of latent locomotor behaviors in mice treated continuously with quinpirole. Neuropsychopharmacology 4:47–55; 1991.