Repeated Quinpirole Treatment: Locomotor Activity, Dopamine Synthesis, and Effects of Selective Dopamine Antagonists

JAMES K. ROWLETT, BRUCE A. MATTINGLY, AND MICHAEL T. BARDO

*Department of Psychology, University of Kentucky, Lexington, Kentucky 40506-0044 (J.K.R., M.T.B.);
Department of Psychology, Morehead State University, Morehead, Kentucky 40351-1689 (B.A.M.)*

KEY WORDS Behavioral sensitization, 3,4-Dihydroxyphenylalanine (DOPA), SCH 23390, Eticlopride, Nigrostriatal pathway, Mesolimbic pathway

ABSTRACT Repeated treatment with the non-selective dopamine agonist apomorphine results in behavioral sensitization and enhanced dopamine synthesis in dopamine projection fields. To examine the role of D_2 -type dopamine receptors in modulating these effects, the present experiment assessed the effects of repeated treatment with the D_2 -type agonist quinpirole on locomotor activity and dopamine synthesis. In the first experiment, rats were treated with vehicle or one of two doses (0.3 or 3.0 mg/kg) of quinpirole for 8 days. Daily measures of locomotor activity revealed an initial suppression of activity produced by quinpirole which dissipated over the 8 days of treatment. A trend for an increase in activity for 3.0 mg/kg quinpirole compared to vehicle was obtained on day 8. Twenty-four hours after cessation of treatment, dopamine synthesis, measured as accumulation of 3,4-dihydroxyphenylalanine (DOPA) after treatment with the DOPA decarboxylase inhibitor NSD-1015, was enhanced in the striatum, but not nucleus accumbens-olfactory tubercle (NAOT) or ventral mesencephalon (VM). In Experiment 2, rats were treated for 8 days with vehicle, 3.0 mg/kg quinpirole or the D_1 antagonist SCH 23390 (0.5 mg/kg) in a two (vehicle or quinpirole) $\times$ two (vehicle or SCH 23390) design. Quinpirole-alone treatment resulted in a reduction of the locomotor suppressant effects of the drug. SCH 23390-alone and quinpirole-SCH 23390 combined treatment resulted in decreased activity compared to the vehicle control group that did not change across days. DOPA accumulation was enhanced in the striatum and NAOT after quinpirole treatment; however, SCH 23390 had no effect. In Experiment 3, rats were treated for 10 days with vehicle, 3.0 mg/kg quinpirole or the D_2 antagonist eticlopride (1.0 mg/kg) in a two (vehicle or quinpirole) $\times$ two (vehicle or eticlopride) design. As in the first two experiments, repeated quinpirole-alone treatment resulted in a reduction of the locomotor suppressant effects of the drug; however, locomotor activity in this group was enhanced compared to vehicle controls on day 10. Eticlopride-alone and eticlopride-quinpirole treated rats had suppressed locomotor activity across the 10 days. DOPA accumulation was enhanced by both repeated quinpirole and repeated eticlopride treatment in the striatum and NAOT. DOPA accumulation in eticlopride-quinpirole treated rats was not different from vehicle control levels in the NAOT, while no significant difference was obtained between the eticlopride-alone and eticlopride-quinpirole groups in the striatum. The locomotor activity data suggest that repeated quinpirole treatment results in tolerance to the locomotor suppressant effect of the drug. Evidence for sensitization was obtained in two out of three of the experiments. These results suggest that enhanced dopamine synthesis after repeated non-selective dopamine agonist treatment is modulated by D_2 -type dopamine receptors. © 1995 Wiley-Liss, Inc.

INTRODUCTION

Drugs that act as direct or indirect agonists for dopamine receptors often produce a progressive enhancement of the acute behavioral effects of the drugs following repeated treatment. This phenomenon is

Received March 21, 1994; accepted in revised form January 31, 1995.

Address reprint requests to Dr. Bruce A. Mattingly, Department of Psychology, Morehead State University, Morehead, KY 40351-1689.

Dr. Rowlett's current address is Department of Psychiatry and Human Behavior, Arthur C. Guyton Laboratory Research Building, The University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216-4505.

Fig. 1. Activity counts (mean $\pm$ SEM) per 20-min session across the 8 days of treatment with quinpirole or vehicle ($n = 13$ rats/group).

and quinpirole versus vehicle treatment. The within-subjects factors were day or brain regions. Violations of homogeneity of variance were examined using the Huyn-Feldt epsilon. Degrees of freedom were corrected if the epsilon value was < 0.75 . Multiple comparisons were made using the Dunnett's test comparing drug groups to the vehicle control or Student's *t*-tests. For the ANOVAs and multiple comparisons, the alpha level was constrained to $P \leq 0.05$.

RESULTS

Experiment 1

Locomotor activity

The locomotor activity data for the 8 days of repeated quinpirole treatment are shown in Figure 1. As may be seen, both doses of quinpirole produced a significant inhibition of locomotor activity on the first treatment day. This inhibitory effect of quinpirole, however, declined with repeated treatments. As expected, a mixed factorial ANOVA revealed a significant main effect of day, $F(7,252) = 8.84$, $P < 0.0001$, and a significant drug dose $\times$ day interaction, $F(14,252) = 10.23$, $P < 0.0001$. To further examine the effect of repeated quinpirole treatment on locomotor activity, an ANOVA was performed on the day 8 data. This analysis revealed a significant effect of drug dose, $F(2,36) = 4.20$, $P < 0.05$; however, Dunnett's tests did not reveal significant differences of the two doses compared to the vehicle controls. These results are consistent with those observed previously in this laboratory using the same procedure (Mattingly et al., 1993).

DOPA accumulation

The DOPA accumulation results of Experiment 1 are shown in Figure 2. A mixed factorial ANOVA revealed a significant main effect of region, $F(2,72) = 209.9$, $P < 0.0001$ and a significant region $\times$ quinpirole dose interaction, $F(4,72) = 3.06$, $P < 0.05$. Multiple comparisons revealed that DOPA levels in the striatum were significantly elevated at both doses of quinpirole compared to control (Dunnett's tests, $P < 0.05$).

Fig. 2. DOPA accumulation (mean percent of vehicle control in $\mu\text{g/g} \pm$ percent SEM for each group) for rats treated 8 days with quinpirole or vehicle ($n = 13$ /group). All rats were treated with NSD-1015 (100 mg/kg) on day 9 prior to dissection of the striatum, NAOT (nucleus accumbens-olfactory tubercle) and VM (ventral mesencephalon). Note that "*" indicates a significant difference from control (Dunnett's tests, $P < 0.05$).

Fig. 3. Activity counts (mean $\pm$ SEM) per 20-min session across the 8 days of treatment with combinations of quinpirole (QUIN, 3.0 mg/kg), SCH 23390 (SCH, 0.5 mg/kg) or vehicle (VEH; $n = 12$ rats/group).

Experiment 2

Locomotor activity

The locomotor activity data for the 8 days of repeated quinpirole-SCH 23390 treatment are shown in Figure 3. As may be seen in this figure, SCH 23390 treatment significantly suppressed locomotor activity and prevented the progressive increase in quinpirole-induced locomotor activity. A mixed factorial ANOVA revealed the following significant between-subjects effects: quinpirole main effect, $F(1,44) = 15.22$, $P < 0.001$; SCH 23390 main effect, $F(1,44) = 272.27$, $P < 0.0001$; quinpirole $\times$ SCH 23390 interaction, $F(1,44) = 22.65$, $P < 0.0001$. The following effects involving repeated measures were significant: day main effect, $F(7,308) = 13.77$, $P < 0.0001$; quinpirole $\times$ day interaction, $F(7,308) = 25.87$, $P < 0.0001$; SCH 23390 $\times$ day interaction, $F(7,308) = 10.69$, $P < 0.0001$; quinpirole $\times$ SCH 23390 $\times$ day interaction, $F(7,308) = 17.68$, $P < 0.0001$. The significant overall interaction likely reflects the grad-

Fig. 4. DOPA accumulation (mean percent of vehicle control in $\mu\text{g/g} \pm$ percent SEM for each group) for rats treated 8 days with combinations of quinpirole (QUIN, 3.0 mg/kg), SCH 23390 (SCH, 0.5 mg/kg) or vehicle (VEH; $n = 12/\text{group}$). All rats were treated with NSD-1015 (100 mg/kg) on day 9 prior to dissection of the striatum, NAOT (nucleus accumbens-olfactory tubercle) and VM (ventral mesencephalon). Note that "*" indicates a significant difference from control (Dunnett's test, $P < 0.05$).

ual increase to control levels by rats treated with vehicle and quinpirole, while all other groups did not change across days. An ANOVA performed on day 8 revealed a significant main effect of SCH 23390, $F(1,44) = 194.42$, $P < 0.0001$. The main effect of quinpirole treatment approached, but did not achieve significance, $F(1,44) = 3.77$, $P = 0.0586$. The interaction of quinpirole and SCH 23390 and all multiple comparisons on day 8 were not significant. These findings also are consistent with our previous study (Mattingly et al., 1993).

DOPA accumulation

The DOPA accumulation results for the three brain regions are shown in Figure 4. A mixed factorial ANOVA revealed significant main effects of quinpirole treatment, $F(1,44) = 14.08$, $P < 0.001$, and region, $F(2,88) = 385.41$, $P < 0.0001$ (epsilon = 0.62). The interaction of region $\times$ quinpirole treatment also was significant, $F(2,88) = 12.32$, $P < 0.001$ (epsilon = 0.62). No main effect or interaction involving SCH 23390 treatment was significant, suggesting that SCH 23390 co-treatment was without effect on DOPA accumulation. Indeed, multiple comparisons revealed that DOPA levels in the vehicle-quinpirole and SCH 23390-quinpirole treated rats were significantly greater than control in both striatum and NAOT (Dunnett's tests, $P < 0.05$). Comparisons of DOPA levels in striatum and NAOT of the vehicle-quinpirole and SCH 23390-quinpirole rats revealed no significant difference (Student's *t*-test, $P > 0.05$).

Experiment 3

Locomotor activity

The locomotor activity data for the 10 days of repeated quinpirole-eticlopride treatment are shown in

Fig. 5. Activity counts (mean $\pm$ SEM) per 20-min session across the 10 days of treatment with combinations of quinpirole (QUIN, 3.0 mg/kg), eticlopride (ETIC, 1.0 mg/kg) or vehicle (VEH; $n = 12$ rats/group).

Figure 5. Like SCH 23390 treatment, eticlopride treatment inhibited locomotor activity and blocked the progressive increase in quinpirole-induced locomotor activity. A mixed factorial ANOVA revealed a significant between-subjects main effect of eticlopride, $F(1,44) = 98.55$, $P < 0.0001$, only. The following effects involving repeated measures were significant: day main effect, $F(9,396) = 4.95$, $P < 0.0001$; quinpirole $\times$ day interaction, $F(9,396) = 13.36$, $P < 0.0001$; eticlopride $\times$ day interaction, $F(9,396) = 3.35$, $P < 0.001$; quinpirole $\times$ eticlopride $\times$ day interaction, $F(9,396) = 5.25$, $P < 0.0001$. An ANOVA performed on day 10 revealed a significant main effect of quinpirole, $F(1,44) = 7.77$, $P < 0.01$, and of eticlopride, $F(1,44) = 41.48$, $P < 0.0001$. The interaction of quinpirole and SCH 23390 on day 10 was not significant. Dunnett's tests showed that the group treated with quinpirole and vehicle had significantly greater locomotor activity counts than the vehicle control group ($P < 0.05$). Thus, after 10 daily treatments, quinpirole significantly increased locomotor activity relative to vehicle control rats. In addition, both groups treated with eticlopride showed significantly lower locomotor activity counts than the controls ($P < 0.05$).

DOPA accumulation

The DOPA accumulation results for the three brain regions are shown in Figure 6. A mixed factorial ANOVA revealed a significant main effect of region, $F(2,86) = 87.72$, $P < 0.0001$ (epsilon = 0.68). No other main effects or interactions were significant. The interaction of quinpirole treatment and eticlopride treatment approached, but did not achieve significance, $F(1,46) = 3.85$, $P = 0.056$. As in Experiment 2, multiple comparisons showed that DOPA accumulation was significantly increased in vehicle-quinpirole treated rats compared to controls in both the striatum and NAOT (Dunnett's tests, $P < 0.05$). Comparisons between controls and the eticlopride-quinpirole treated rats re-

Fig. 6. DOPA accumulation (mean percent of vehicle control in $\mu\text{g/g} \pm$ percent SEM for each group) for rats treated 10 days with combinations of quinpirole (Q, 3.0 mg/kg), eticlopride (E, 1.0 mg/kg) or vehicle (n = 12/group). All rats were treated with NSD-1015 (100 mg/kg) on day 11 prior to dissection of the striatum, NAOT (nucleus accumbens-olfactory tubercle) and VM (ventral mesencephalon). Note that * ** indicates a significant difference from control (Dunnett's test, $P < 0.05$).

revealed a significant increase in DOPA accumulation for the striatum, but not NAOT (Dunnett's tests, $P < 0.05$). However, DOPA levels also were elevated in the eticlopride-vehicle treated rats compared to controls in both striatum and NAOT (Dunnett's tests, $P < 0.05$). Additional t-tests comparing eticlopride-vehicle and eticlopride-quinpirole rats revealed no significant differences.

DISCUSSION

Consistent with our previous findings, acute quinpirole treatment resulted in dose-dependent suppression of locomotor activity (Mattingly et al., 1993). With repeated treatment, the locomotor suppressant effect of quinpirole diminished until the activity levels of quinpirole-treated rats were equal to (Experiments 1 and 2), or greater than (Experiment 3), vehicle-treated rats. This progressive increase in quinpirole-induced locomotor activity is consistent with our previous work (Mattingly et al., 1993). Within the present paradigm, whether this increase in quinpirole-induced activity should be interpreted as tolerance or sensitization is unclear. However, previous work in other laboratories using longer test intervals has demonstrated a biphasic inhibitory-excitatory effect of quinpirole following a single administration and a clear sensitization effect with repeated administration (Eilam et al., 1992). Similarly, the direct D_2 -type dopamine receptor agonist bromocryptine also depressed locomotor activity when first presented, but resulted in locomotor sensitization with repeated treatment (Hoffman and Wise, 1992). Thus, the lack of a clear sensitization effect in the present study may be related to the relatively short duration of the activity test used.

The major finding of the present experiment was that repeated quinpirole treatment resulted in enhanced DOPA accumulation in the striatum and NAOT. Thus, consistent with previous studies with repeated apomorphine treatment (Rowlett et al., 1991, 1993; Vaughn et al., 1990), repeated stimulation of D_2 -type dopamine receptors resulted in enhanced dopamine synthesis in dopamine terminal fields. We have previously noted that enhanced dopamine synthesis in the NAOT following repeated apomorphine treatment may be a relatively weak effect compared to the effect obtained in the striatum (Rowlett et al., 1993). Some evidence for a similar relationship between dopamine synthesis in the NAOT and striatum following repeated quinpirole was obtained in the present series of experiments. Thus, while striatal dopamine synthesis was clearly increased in all three experiments, the enhanced dopamine synthesis effect was obtained in the NAOT only in Experiments 2 and 3, but not Experiment 1. Moreover, the magnitude of the percentage increase in DOPA accumulation in the NAOT varied from experiment to experiment, whereas the magnitude of the percentage increase in DOPA accumulation in the striatum was relatively consistent across experiments. The reason for this difference in DOPA accumulation results between the striatum and NAOT is not clear; however, the results may reflect a differential modulation of dopamine synthesis between the striatum and NAOT.

Experiment 2 demonstrated that co-administration of the selective D_1 receptor antagonist SCH 23390 did not block the enhanced dopamine synthesis effect produced by repeated quinpirole treatment. This finding is consistent with modulation of dopamine synthesis by D_2 autoreceptors, and not D_1 -type receptors (Brown et al., 1985; Wachtel et al., 1989; White and Wang, 1984b; Wolf and Roth, 1990). Further, this finding is consistent with a previous study which indicated that D_1 receptor stimulation does not result in enhanced dopamine synthesis (Rowlett et al., 1993). The results of Experiment 3 suggest that the D_2 -type antagonist eticlopride blocked the enhanced dopamine synthesis effect produced by quinpirole in the NAOT. This finding is consistent with eticlopride's high selectivity for D_2 -type receptors and provides further evidence for D_2 -type modulation of the enhanced dopamine synthesis effect. In the striatum, there was no significant difference in DOPA accumulation between the eticlopride-vehicle and eticlopride-quinpirole treated rats, also suggestive of a blockade of the enhanced dopamine synthesis effect produced by repeated quinpirole treatment. However, dopamine synthesis was enhanced following repeated eticlopride treatment in both striatum and NAOT. This finding was unexpected and the reason for this enhanced dopamine synthesis effect following repeated eticlopride treatment is not clear. One possibility is that eticlopride was present in the brain at the time of NSD-1015 administration. Support for this

notion comes from previous findings that acute eticlopride treatment produces enhanced DOPA accumulation (Tyler and Galloway, 1992) and D_2 -type antagonists produce enhanced dopamine neuron impulse flow (White and Wang, 1984b). Indeed, O'Dell et al. (1993) reported that repeated eticlopride treatment (four injections at 2-h intervals) resulted in enhanced striatal dopamine release, measured with in vivo microdialysis. It is also possible, however, that repeated eticlopride treatment resulted in some neurochemical alteration that indirectly enhanced dopamine synthesis. For example, repeated eticlopride treatment results in up-regulation of D_2 -type receptors (LaHoste and Marshall, 1991); however, up-regulation of autoreceptors would likely result in decreased dopamine synthesis. These issues clearly require further investigation; nevertheless, evidence for a blockade of repeated quinpirole-induced enhanced dopamine synthesis in the NAOT clearly was obtained, in spite of the increase in DOPA accumulation produced by repeated eticlopride alone.

The observation of an enhanced dopamine synthesis effect after repeated quinpirole treatment is consistent with the notion that repeated non-selective dopamine agonist treatment produces a reduction in dopamine autoreceptor sensitivity (e.g., Henry et al., 1989; Jezioriski and White 1989; Rebec and Lee, 1982; Rowlett et al., 1991, 1993; White and Wang, 1984a). Indeed, the results of this study combined with our previous findings indicate that the enhanced dopamine synthesis effect observed after repeated apomorphine treatment likely is modulated by D_2 -type autoreceptors. Taken together, our findings are consistent with an hypothesis for the development of behavioral sensitization advanced by Henry et al. (1989). Specifically, these authors suggested that repeated cocaine treatment results in subsensitivity of impulse-regulating autoreceptors followed by terminal field D_1 receptor supersensitivity. The results of the present study and our previous study (Mattingly et al., 1993) showing cross-sensitization of quinpirole and apomorphine that was blocked by a D_1 antagonist are consistent with this hypothesis. Thus, repeated quinpirole treatment may result in autoreceptor subsensitivity, which in turn results in enhanced dopamine release and consequent D_1 stimulation. In the present study, blockade of D_1 receptors had no effect on dopamine synthesis after repeated quinpirole treatment. Therefore, autoreceptor subsensitivity may occur without the development of locomotor sensitization.

Recent molecular biological studies have identified at least five subtypes of dopamine receptors (see Schwartz et al., 1993). Of these subtypes, quinpirole binds with higher affinity to the D_3 subtype than to the D_2 or D_4 subtypes, whereas apomorphine is relatively non-selective for the D_2 subtypes (Levesque et al., 1992; Sokoloff et al., 1990; Van Tol et al., 1991). Based upon this affinity difference, it may be speculated that the enhanced

dopamine synthesis effect observed after repeated quinpirole and apomorphine treatment may involve repeated D_3 receptor stimulation. However, it is not known if the doses used in the present study differentiate between the two subtypes. In addition, the most robust augmentation of dopamine synthesis occurred in the striatum, an area that has low levels of D_3 mRNA, as well as low binding levels of the D_3 ligand [3H]7-OH-DPAT (Levesque et al., 1992; Schwartz et al., 1993; Sokoloff et al., 1990). Thus, the role of D_3 versus D_2 receptors in the enhanced dopamine synthesis effect remains to be determined.

Finally, another possible mechanism of enhanced dopamine synthesis following repeated apomorphine treatment involves an alteration of tyrosine hydroxylase activity. Apomorphine, in addition to having dopamine receptor binding properties, also may be carried into dopamine neurons where it inhibits tyrosine hydroxylase activity directly at the pteridine cofactor site (Laschinski et al., 1984). Based on the results of the present study, however, this effect of apomorphine may not be involved in the enhanced dopamine synthesis effect because quinpirole does not have a catechol structure (Titus et al., 1983). Thus, any changes in tyrosine hydroxylase activity following repeated D_2 agonist treatment are likely due to an indirect influence on the enzyme rather than direct drug-induced changes at the pteridine cofactor site.

ACKNOWLEDGMENTS

This research was supported in part by grants from the Kentucky EPSCoR Committee and Morehead State University. The authors are grateful to Tracey Ellison, Sonia Fields, Steve McDonald, and Kristin Rase for assistance with behavioral testing, and to Melinda Bradley for assistance with the neurochemical experiments. This research was supported in part by USPHS grant DA 05312.

REFERENCES

- Brown, F., Campbell, W., Mitchell, P.J., and Randall, K. (1985) Dopamine autoreceptors and the effects of drugs on locomotion and dopamine synthesis. *Br. J. Pharmacol.*, 84:853-860.
- Castro, R., Abreu, P., Calzadilla, C.H., and Rodrigues, M. (1985) Increased or decreased locomotor response in rats following repeated administration of apomorphine depends on dosage interval. *Psychopharmacology*, 85:333-339.
- Eilam, D., Talangbayan, H., Dai, H., Canaran, G., and Szechtman, H. (1992) Profile of behavioral changes during the course of chronic treatment with D-2 agonist quinpirole. *Soc. Neurosci. Abstr.*, 18: 887.
- Henry, D.J., Greene, M.A., and White, F.J. (1989) Electrophysiological effects of cocaine in the mesoaccumbens dopamine system: repeated administration. *J. Pharmacol. Exp. Ther.*, 258:833-839.
- Hoffman, D.C., and Wise, R.A. (1992) Locomotor-activating effects of the D_2 agonist bromocriptine show environment-specific sensitization following repeated injections. *Psychopharmacology*, 107:277-284.
- Jezioriski, M., and White, F.J. (1989) Dopamine agonists at repeated "autoreceptor-selective" doses: effects upon the sensitivity of A10 dopamine autoreceptors. *Synapse*, 4:267-280.
- Kalivas, P.W., and Stewart, J. (1991) Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. *Brain Res. Rev.*, 16:223-244.

- Karler, R., Calder, L.D., and Turkianis, S.A. (1991) DNQX blockade of amphetamine behavioral sensitization. *Brain Res.*, 552:295-300.
- Kuczenski, R., and Leith, N.J. (1981) Chronic amphetamine: is dopamine a link or a mediator of the development of tolerance and reverse tolerance? *Pharmacol. Biochem. Behav.*, 15:405-413.
- LaHoste, G.J., and Marshall, J.F. (1991) Chronic eticlopride and dopamine denervation induce equal nonadditive increases in striatal D2 receptor density: autoradiographic evidence against the dual mechanism hypothesis. *Neuroscience*, 41:473-481.
- Laschinski, G., Kittner, B., and Brautigam, M. (1984) Inhibition of striatal tyrosine hydroxylase by low concentrations of apomorphine. *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 327:114-118.
- Levesque, D., Diaz, J., Pilon, C., Martres, M.-P., Giros, B., Souil, E., Schott, D., Morgat, J.-L., Schwartz, J.-C., and Sokoloff, P. (1992) Identification, characterization, and localization of the dopamine D₃ receptor in rat brain using 7-[3H]hydroxy-N,N-di-n-propyl-2-aminotetralin. *Proc. Natl. Acad. Sci. U.S.A.*, 89:8155-8159.
- Mattingly, B.A., and Rowlett, J.K. (1989) Effects of repeated apomorphine and haloperidol treatments on subsequent sensitivity to apomorphine. *Pharmacol. Biochem. Behav.*, 34:345-347.
- Mattingly, B.A., Gotsick, J.E., and Marin, C. (1988a) Locomotor activity and stereotypy in rats following repeated apomorphine treatments at 1-, 3- or 7-day intervals. *Pharmacol. Biochem. Behav.*, 31:871-875.
- Mattingly, B.A., Gotsick, J.E., and Salamanca, K. (1988b) Latent sensitization to apomorphine following repeated low doses. *Behav. Neurosci.*, 102:553-558.
- Mattingly, B.A., Rowlett, J.K., Graff, J.T., and Hatton, B.J. (1991) Effects of selective D₁ and D₂ dopamine antagonists on the development of behavioral sensitization to apomorphine. *Psychopharmacology*, 105:501-507.
- Mattingly, B.A., Rowlett, J.K., and Lovell, G. (1993) Effects of daily SKF 38393, quinpirole, and SCH 23390 treatments on locomotor activity and subsequent sensitivity to apomorphine. *Psychopharmacology*, 110:320-326.
- O'Dell, S.J., Weihmuller, F.B., and Marshall, J.F. (1993) Methamphetamine-induced dopamine overflow and injury to striatal dopamine terminals: attenuation by dopamine D₁ and D₂ antagonists. *J. Neurochem.*, 60:1792-1799.
- Paxinos, F., and Watson, C. (1986) *The Rat Brain in Stereotaxic Coordinates*, 2nd ed. Academic Press, New York.
- Peris, J., and Zahniser, N.R. (1989) Persistent augmented dopamine release after acute cocaine requires dopamine receptor activation. *Pharmacol. Biochem. Behav.*, 32:71-76.
- Rebec, G.V., and Lee, E.H. (1982) Differential subsensitivity of dopaminergic and neostriatal neurons to apomorphine with long-term treatment. *Brain Res.*, 250:188-192.
- Robinson, T.E., and Becker, J.B. (1986) Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. *Brain Res. Rev.*, 11:157-198.
- Rowlett, J.K., Mattingly, B.A., and Bardo, M.T. (1991) Neurochemical and behavioral effects of acute and chronic treatment with apomorphine in rats. *Neuropharmacology*, 30:191-197.
- Rowlett, J.K., Mattingly, B.A., and Bardo, M.T. (1993) Neurochemical correlates of behavioral sensitization following repeated apomorphine treatment: assessment of the role of D₁ dopamine receptor stimulation. *Synapse*, 14:160-168.
- Schwartz, J.-C., Levesque, D., Martres, M.-P., and Sokoloff, P. (1993) Dopamine D₃ receptor: basic and clinical aspects. *Clin. Neuropharmacology*, 4:295-314.
- Sokoloff, P., Giros, B., Martres, M.-P., Bouthenet, M.-L., and Schwartz, J.-C. (1990) Molecular cloning and characterization of a novel dopamine receptor (D₃) as a target for neuroleptics. *Nature*, 347:146-151.
- Titus, R.D., Kornfield, E.C., Jones, N.D., Clemens, J.A., Smalstig, E.B., Fuller, R.W., Hahn, R.A., Hynes, M.D., Mason, N.R., Wong, D.T., and Foreman, M.M. (1983) Resolution and absolute configuration of an ergoline related dopamine agonist, trans-4,4a,5,6,7,8,8a,9-octahydro-5-propyl-1H(or 2H)-pyrazolo [3,4-g] quinoline. *J. Med. Chem.*, 26:1112-1116.
- Tyler, C.B., and Galloway, M.P. (1992) Acute administration of amphetamine: differential regulation of dopamine synthesis in dopamine projection fields. *J. Pharmacol. Exp. Ther.*, 261:567-573.
- Van Tol, H.H.M., Bunzow, J.R., Guan, H.-C., Sunahara, R.K., Seeman, P., Niznik, H.B., and Civelli, O. (1991) Cloning of the gene for a human dopamine D₄ receptor with high affinity for the antipsychotic clozapine. *Nature*, 350:610-614.
- Vaughn, D.M., Severson, J.A., Woodward, J.J., Randall, P.K., Riffe, W.H., Leslie, S.W., and Wilcox, R.E. (1990) Behavioral sensitization following subchronic apomorphine treatment-possible neurochemical basis. *Brain Res.*, 526:37-44.
- Wachtel, S.R., Hu, X.-T., Galloway, M.P., and White, F.J. (1989) D₁ dopamine receptor stimulation enables the postsynaptic, but not autoreceptor, effects of D₂ agonists in the nigrostriatal and mesocumbens dopamine systems. *Synapse*, 4:327-346.
- Westerink, B.H.C., and Korf, J. (1976) Comparison of effects of drugs on dopamine metabolism in the substantia nigra and the corpus striatum of the rat brain. *Eur. J. Pharmacol.*, 40:131-136.
- White, F.J., and Wang, R.Y. (1984a) Electrophysiological evidence for A10 dopamine autoreceptor subsensitivity following chronic d-amphetamine treatment. *Brain Res.*, 309:283-292.
- White, F.J., and Wang, R.Y. (1984b) Pharmacological characterization of dopamine autoreceptors in the rat ventral tegmental area: microiontophoretic studies. *J. Pharmacol. Exp. Ther.*, 231:275-280.
- Wise, R.A., and Carlezon, W.A., Jr. (1994) Attenuation of the locomotor-sensitizing effects of the D₂ dopamine agonist bromocriptine by either the D₁ antagonist SCH 23390 or the D₂ antagonist raclopride. *Synapse*, 17:155-159.
- Wolf, M.E., and Roth, R.H. (1990) Autoreceptor regulation of dopamine synthesis. In: *Presynaptic Receptors and the Question of Autoregulation of Neurotransmitter Release*. S. Kalsner and T.C. Westfall, eds. *Annals of the New York Academy of Sciences*, 604:323-343.
- Wolf, M.E., White, F.J., Nassar, R., Brooderson, R.J., and Khansa, M.R. (1993) Differential development of autoreceptor subsensitivity and enhanced dopamine release during amphetamine sensitization. *J. Pharmacol. Exp. Ther.*, 264:249-255.
- Zahniser, N.R., Peris, J., Dwoskin, L.P., Curella, P., Yasuda, R.P., O'Keefe, L., and Boyson, S.J. (1988) Sensitization to cocaine in the nigrostriatal dopamine system. In: *National Institute on Drug Abuse Research Monograph 88*. D. Clouet, K. Asghar, and R. Brown, eds. U.S. Government Printing Office, Washington, D.C.