Pharmacology Biochemistry and Behavior, Vol. 63, No. 1, pp. 55–61, 1999

0091-3057/99/$–see front matter

PII S0091-3057(98)00234-2

Dopamine Antagonists in the Orbital Prefrontal Cortex Reduce Prepulse Inhibition of the Acoustic Startle Reflex in the Rat

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Received 10 April 1998; Revised 9 September 1998; Accepted 5 October 1998

ZAVITSANOU, K., J. CRANNEY AND R. RICHARDSON. *Dopamine antagonists in the orbital prefrontal cortex reduce prepulse inhibition of the acoustic startle reflex in the rat.* PHARMACOL BIOCHEM BEHAV **63**(1) 55–61, 1999.—Schizophrenia is characterized by, among other things, (a) information processing deficits that have been indexed by a number of measures, including deficits in prepulse inhibition (PPI) of the acoustic startle reflex; and (b) pathophysiology of the frontal lobe. Recent studies have implicated the prefrontal cortex (PFC) in the modulation of PPI in rats. These studies suggest that dopamine (DA) ablation of the PFC (using 6-OHDA) leads to disruption of PPI. To better understand the role of DA type 1 (D_1) and type 2 (D_2) receptors in the modulation of PPI, we investigated the effects of two pharmacologically distinct DA antagonists on the modulation of PPI. Microinjection of SCH23390 (a D_1 antagonist) into the orbital PFC markedly decreased PPI (at 0.1, 0.5, and 1.5 μg), whereas raclopride (a D_2 antagonist) decreased PPI at some doses (0.1 and 0.5 mg/ml) but not at others (5.0 μg). We conclude that both D_1 and D_2 receptors mediate the cortical modulation of PPI. © 1999 Elsevier Science Inc.

Dopamine antagonists Prepulse inhibition Prefrontal cortex Schizophrenia

PREPULSE inhibition (PPI) of the acoustic startle reflex (ASR) occurs when a weak, nonstartle-eliciting stimulus (prepulse), presented 30–500 ms before the startle-eliciting acoustic stimulus, results in the reduction of ASR amplitude (18, 20). The inhibitory processes activated by the prepulse and the resulting decrement in startle amplitude is thought to represent a behavioral model for sensorimotor gating (41,43). Braff et al. (4) reported that PPI is impaired in schizophrenic patients, and suggested that this deficit in sensorimotor gating reflects the disrupted attentional processing characteristic of schizophrenia. The disruption of PPI observed in rats after a variety of manipulations may, in some circumstances, constitute a viable animal model for delineating the anatomical and neurochemical bases of the sensorimotor gating deficit observed in schizophrenia (41,43,48).

One hypothesis regarding the neural bases of schizophrenia is that there is overactivity of the mesolimbic dopamine (DA) projection system (23) that involves projections from the Ventral tegmental area (VTA) to the nucleus accumbens (Acb) (3). In considering the role of dopamine in schizophrenia, it is relevant to note that dopamine receptors are usually classified into two main groups on the basis of ligand-binding pharmacology and amino acid homology (35). The D_1-like receptors include types D_1 and D_5, while the D_2-like receptors include types D_2, D_3, and D_4. Several studies have shown that manipulations that should lead to an increase in Acb D_2-like activity in rats leads to deficits in PPI (50,51).

Another hypothesis regarding the neural bases of schizophrenia is that there are structural and functional abnormalities in the prefrontal cortex (23). The prefrontal cortex (PFC) is defined as the cortical projection field of the mediodorsal thalamic nucleus (33), and comprises: (a) a medial division (mPFC), including the medial precentral, dorsal anterior cingulate, and prelimbic cortices; (b) a ventromedial division that has been recently added, (14); (c) a ventral orbital division; and (d) a sulcal division, called the agranular insular cortex, situated within the rhinal sulcus [cortical terminology according to (27); see also (38)]. Further, a convergence has been demonstrated within the prefrontal cortex of projections from DA-containing neurons located in the VTA (i.e., the mesocortical DA system) and of projections from neurons within the mediodorsal thalamic nucleus (2,10).

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Several studies with rats have examined the role of prefrontal cortex in the modulation of PPI. Briefly, NMDA or ibotenic acid lesions of the mPFC, as well as infusion of DA in the orbital PFC, have no effect on PPI (28,42,45). In contrast, manipulations of the mPFC that lead to decreased PFC DA activity, such as 6-OHDA lesions (5,24) or infusion of specific D_1- or D_2-like antagonists, significantly reduce PPI (12). This finding may relate to studies in humans that suggest that abnormal activity of the prefrontal cortex in schizophrenic patients may be the result of decreased activity of the cortical D_1-like receptor system [see (23)]. Thus, the research with animal models indicates that lowered DA activity in the PFC has the same effect on PPI as does heightened DA activity in the Acb: in both cases, PPI is disrupted. These sets of findings suggest the hypothesis that the cognitive disturbances observed in schizophrenia are mediated by functional overactivity of the mesolimbic DA projection system, and/or functional underactivity of the mesocortical DA system (22,23). Specific schizophrenic symptoms may be associated with specific dysfunction of either the Acb or the PFC; however, it is likely that the sensorimotor gating deficit, indexed by decreased PPI, is the direct result of Acb DA overactivity. That is, the PPI deficit that occurs with PFC dysfunction may not be a direct effect, but rather an indirect effect mediated by the consequent overactivity of the Acb.

As yet, the role of specific PFC subregions in the DA modulation of PPI has not been extensively investigated. At least two subregions of the PFC, the medial and orbital parts, are functionally dissociable. For example, the mPFC is involved in learning tasks with spatial and/or temporal cues, and social behavior (7,15,26), whereas the orbital PFC is involved in certain social and emotional behaviors such as suppression of aggression (7). Moreover, the medial and orbital PFC project to different cortical, striatal, basal forebrain, thalamic, and brain stem subregions [see (26), for a detailed review]. From this, it is possible that DA modulation of PPI is localized within specific PFC subregions. Previously, Ellenbroek et al. (12) found that infusion of SCH39166 (a D_1-like antagonist) and sulpiride (a D_2-like antagonist) in the mPFC disrupted PPI. In the current study, we measured PPI after local injection of two pharmacologically distinct dopamine antagonists in the orbital part of PFC. Raclopride was used as the selective D_2-like antagonist, and SCH23390 was used as the selective D_1-like receptor antagonist. If the orbital PFC is an anatomical locus of the modulation of PPI, like the mPFC appears to be, then animals given a DA-specific antagonist should exhibit disruption of PPI; if D_1- or D_2-receptor subtypes in the orbital PFC are differentially involved in sensorimotor gating, then PPI should be disrupted following infusion of one antagonist but not the other.

METHOD

Subjects

Adult male Sprague–Dawley-derived rats, weighing between 299 and 439 g at the time of surgery, were used as subjects. Prior to surgery (see below) animals were group housed with eight per plastic cage (65 × 40 × 22 cm; L × W × H); after surgery, animals were singly housed in a plastic cage (27 × 24.5 × 37 cm). At all times food and water were available ad lib, and animals were maintained on a natural light–dark cycle. Testing took place during the light portion of the cycle. Animals were handled for 3–5 min a day for at least 3 days prior to surgery and for 1–2 min every day postoperatively. Seventy-five rats were tested in this study, but the data from 16 rats were discarded on histological grounds (see below). All experimental procedures followed the Policy on the Use of Animals in Neuroscience Research, adopted by the Society for Neuroscience (USA), and were approved by the Animal Care and Ethics Committee at the University of New South Wales.

Surgery

Anesthesia was induced by an injection (IP) of a mixture of ketamine (1.33 mg/kg; Ketapex, 100 mg/ml) and xylazine (6.6 mg/kg; Rompun, 20 mg/ml). A single guide cannula (22 gauge; Plastics One, Roanoke, VA) was implanted in the right hemisphere using these coordinates: A/P +4.5 mm from bregma, L +0.7 mm from the midline, and D/V −4.9 mm from the skull (31). The cannula was fitted with a stylet, and a 7–10-day recovery period was provided before any behavioral testing.

Drugs

Hamilton microsyringes and a microinfusion pump (Harvard Apparatus) were used to intracerebrally infuse either the D_1-like antagonist SCH23390 (RBI), the D_2-like antagonist raclopride (Astra Arcus), or saline. All drugs were made fresh daily, and three doses of each drug were tested in independent groups. Specifically, some groups received 0.1 μg (n = 9), 0.5 μg (n = 8), or 1.5 μg (n = 10) of SCH23390, while others received 0.5 μg (n = 7), 1.5 μg (n = 9), or 5.0 μg (n = 5) of raclopride (all in a volume of 0.5 μl). The control group (n = 11) received an equivalent volume of the vehicle (i.e., normal saline). Infusions were made by replacing the stylet with a microsyringe needle that extended 1-mm beyond the tip of the guide cannula. Infusions were given over a 1-min period, and the infusion needle remained in place for an additional minute to allow for diffusion of the drug. Before behavioral testing the injector needles were removed and replaced with the stylets.

Startle Cages

All behavioral tests occurred in one of two identical startle chambers (20 × 12 × 13 cm). The floor and the two side walls of each chamber were made of 3-mm stainless steel rods spaced 13 mm apart; the rest of each chamber was made of clear Plexiglas. Each startle cage was suspended from a large sheet of Plexiglas to which a piece of piezoelectric film had been laminated. Movements within the startle cage produced flexion in the Plexiglas sheet that resulted in a voltage being produced by the piezoelectric film; this voltage was proportional to the magnitude of the movement—larger, more intense movements produced larger voltages. This voltage was amplified and digitized (at a 1-kHz rate) by a custom-built unit during a 250-m period, beginning at the onset of each startle stimulus. The largest response measured during any single millisecond of this period was used as the measure of the subject's startle response. Each startle chamber was housed in a sound- and light-attenuating cabinet. In each cabinet, illumination was provided by a 25-W red light on the front door, and a ventilation fan provided a 60-dB background noise at all times (scale A, slow, on a type 2335 Bruel and Kjaer sound level meter).

Acoustic Stimuli

To elicit the startle response a 120-dB (peak), 50-ms white-noise burst was used. To produce prepulse inhibition of startle, a 20-ms white noise burst was presented 80-ms before the

startle stimulus. On some trials the prepulse was 3 dB above background (low prepulse), while on others it was 35 dB above background (high prepulse); more inhibition should be observed with the more intense prepulse. All acoustic stimuli were presented by two piezoelectric speakers, wired in parallel, mounted 8 cm from either side of the startle cage.

Testing Procedure

Immediately after the infusion treatment had ended each animal was placed in a startle cage. Following a 2-min adaptation period the test session, consisting of 50 trials, began. The first and last trial involved presenting the startle stimulus alone, while the other 48 trials were comprised of four blocks of 12 trials. Each of these blocks consisted of four trial types: (a) startle stimulus alone—four trials; (b) startle stimulus preceded by the low prepulse—three trials; (c) startle stimulus preceded by the high prepulse—three trials; and (d) no stimulus—two trials. Within each block, the various trial types were presented in a pseudorandom order (no more than two trials of the same type in a row). Trials were separated by a variable intertrial interval (average = 20 s; range = 15–25 s). Data collection and the timing of all stimulus presentations was computer controlled with custom-designed software.

Histology

Following completion of the behavioral test, animals were injected with Nembutal and decapitated. Brains were removed and frozen sections 40 mm thick were cut, collected on slides, and stained with cresyl violet. Histological analysis revealed either extensive tract damage or that the cannula tip was located outside the target area in 16 animals; the data from these animals were not included in the statistical analysis. The location of the cannula tips for the 59 animals whose data were included in the analysis is shown in Fig. 1.

RESULTS

Data Analysis Procedures

The mean response for each trial type (collapsed across the four blocks of test trials) was determined for every animal. To assess prepulse inhibition of startle, a percentage score was derived with the following formula: [(mean response on startle alone trials − mean response on prepulse trials)/mean response on startle alone trials] × 100. Larger scores indicate more prepulse inhibition. Percent inhibition was determined separately for the low and the high prepulses. Although all the data was collected concurrently, two separate sets of ANOVAs were undertaken: (a) one examining the effects of the D_1-like antagonist SCH23390, and (b) one examining the D_2-like antagonist raclopride. The same saline control group was used in each of these analyses. Pairwise comparisons were made with the least significant difference test ($p < 0.05$).

Baseline and Blank Trials

Any drug effects on general activity or the startle response itself would be revealed by the responses on the blank and startle-alone trials, respectively. As can be seen in Table 1, there were no obvious group differences on either of these trial types—indicating that neither drug affected general activity or startle amplitude. Statistical analysis, by a one-way ANOVA with treatment as a factor, showed that neither SCH23390 nor raclopride affected responding on the blank trials, $F(3, 34) = 1.12$, and $F(3, 28) = 2.11$, respectively; both ps > 0.10, or the startle-alone trials, $F(3, 34) = 1.65$, and $F(3, 28) = 1.29$, respectively; both ps > 0.10.

We also analyzed the baseline startle response data with trial block as a factor. This analysis revealed that the startle response habituated across the four trial blocks, but that neither of the two antagonists exerted a systematic effect on this.

Prepulse Inhibition of Startle

As reported in other studies, the more intense prepulse caused more inhibition than the less intense prepulse [for review, see (17)]. Of more interest, it appears that infusion of either SCH23390 or raclopride into the prefrontal cortex reduced the amount of prepulse inhibition produced by the low, but not the high, prepulse (see Fig. 2).

We also analyzed the PPI results with trial block as a factor. This analysis revealed that the amount of PPI increased over trial blocks, but that neither of the two antagonists exerted a systematic effect on this. The only deviation in these analyses was that the group given 5.0 μg of raclopride exhibited significantly more PPI on trial block 1 than did the groups given the low or moderate dose of raclopride.

Effects of SCH23390. Analysis of variance showed that SCH23390 significantly reduced the prepulse inhibition produced by the low prepulse, $F(3, 34) = 9.81$, $p < 0.01$, but had no effect on the prepulse inhibition produced by the high prepulse, $F(3, 34) = 2.01$, $p > 0.10$. Post hoc pairwise comparisons showed that all three groups given SCH23390 exhibited significantly less prepulse inhibition to the low prepulse than did the saline controls. Further, the three drug-treated groups did not differ from one another (see the left panel of Fig. 2).

Effects of raclopride. Analysis of variance showed that raclopride significantly reduced the prepulse inhibition produced by the low prepulse, $F(3, 28) = 3.77$, $p < 0.05$, but had no effect on the prepulse inhibition produced by the high prepulse ($F < 1.0$). Post hoc pairwise comparisons showed that disruption of inhibition to the low prepulse by raclopride was dose dependent: the groups given either 0.5 or 1.5 μg of raclopride showed a significant disruption of PPI, but those given 5.0 μg did not (see the right panel of Fig. 2).

DISCUSSION

Implications of Findings

The results of this study show that infusion in the PFC of either SCH23390 or raclopride, selective D_1 and D_2 antagonists, respectively, cause a decrement in PPI to a low (3 dB above background), but not a high (35 dB above background), prepulse stimulus. However, it must be noted that the high intensity prepulse in the present study may have elicited a startle response on some trials. That is, the attenuation of the startle response to the test stimulus in this condition may have been due to a refractory period rather than sensorimotor gating [e.g., (21)]. Nonetheless, the finding that DA antagonists in the prefrontal cortex leads to reduced PPI to a low intensity prepulse is consistent with (a) results showing that 6-OHDA lesions of the PFC reduce PPI (5,24), and (b) Ellenbroek et al.'s (12) recent study showing that local infusion of either SCH39166 or sulpiride, selective D_1-like and D_2-like antagonists, respectively, into the PFC reduces PPI.

The study by Ellenbroek et al. (12) is very similar conceptually to the current study, but there are some notable procedural differences between the two studies. First, Ellenbroek et al. (12) used different antagonists than those used in the present study (i.e., SCH39166 vs. SCH23390 as the D_1-like an-

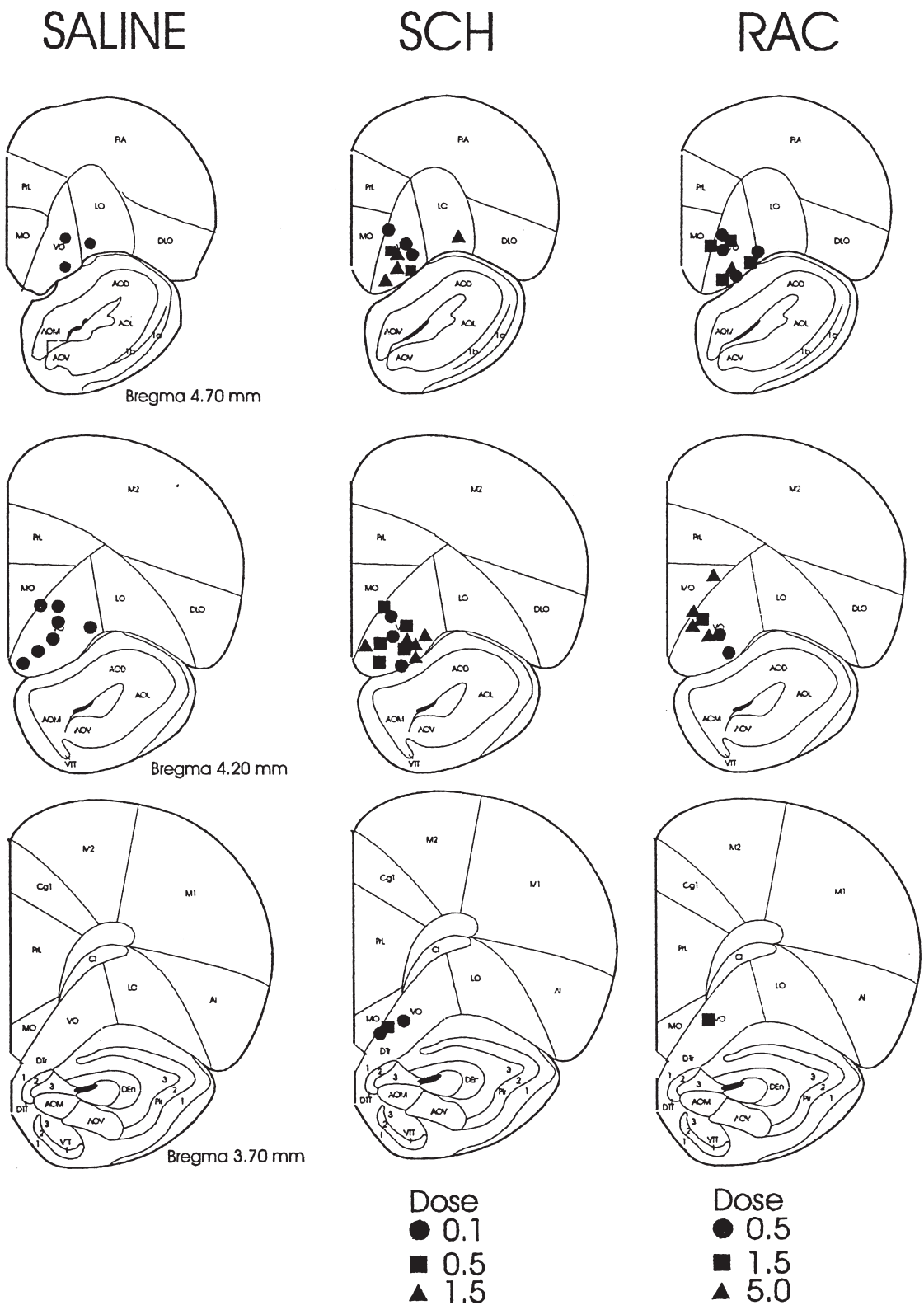

FIG. 1. Placement of cannula tips for each of the dosages (μg) of raclopride (RAC), SCH23390 (SCH), and saline groups, using coronal plates from Swanson (39). Some points represent more than one cannula tip placement.

TABLE 1

MEAN RESPONSES (± SEM) ON BLANK AND STARTLE ALONE TRIALS FOR ANIMALS GIVEN INFUSIONS OF EITHER SALINE, SCH23390, OR RACLOPRIDE IN THE PREFRONTAL CORTEX

Trial Type	Saline	0.1 μg SCH23390	0.5 μg SCH23390	1.5 μg SCH23390	0.5 μg Raclopride	1.5 μg Raclopride	5.0 μg Raclopride
Blank	5.64	7.78	5.75	5.2	5.86	8.44	5.4
	(.82)	(1.6)	(.65)	(.98)	(.67)	(1.0)	(.82)
Startle alone	235	270	293	261	273	238	199
	(20)	(10)	(7)	(25)	(17)	(16)	(45)

tagonist and sulpiride vs. raclopride as the D_2-like antagonist). Second, Ellenbroek et al. made local infusions into the prelimbic area of the medial PFC, whereas we made local infusions into the orbital part of the PFC. Third, Ellenbroek et al. made bilateral infusions, whereas the present study made unilateral infusions in the right hemisphere. Interestingly, other studies have reported that unilateral lesions of the medial prefrontal cortex differentially affected subcortical dopamine utilization and the behavioral response to stress (6). In the current study, however, the physical proximity of the orbital PFC to midline allows for the possibility that the infused antagonists diffused to the left hemisphere. It will be important for future research in this area to explicitly compare the effects of bilateral/unilateral infusions of DA antagonists into PFC. In any case, given the procedural differences between the current study and that of Ellenbroek et al. (12), it is reassuring that comparable results were obtained in both studies, as it suggests that modulation of sensorimotor gating by DA activity in the PFC is a robust effect.

One puzzling aspect of the present results involves the failure of the high dose of raclopride to disrupt PPI (see the right panel of Fig. 2). This result could be related to the small sample size ($n = 5$) of that group, or could be due to some pharmacokinetic effect leading to a nonlinear pattern of results (a not unexpected finding in drug research). One possible explanation along these lines is that the high dose of raclopride diffused throughout the brain and blocked subcortical receptors (we would like to acknowledge that an anonymous reviewer suggested this possibility). This would oppose the effects of prefrontal dopamine blockade by the mechanisms outlined below. This interpretation of the failure of the high dose of raclopride to disrupt PPI is also supported by the fact that raclopride is a D_2-like antagonist and the subcortical modulation of PPI is specific to the D_2-like receptor system (50,51).

Possible Mechanism of Disruption of PPI

Although multiple neurotransmitter and anatomical systems are involved in the modulation of PPI [(25), for a review], one major cause of PPI disruption is overactivity of subcortical dopamine (40,43,44). The question then arises as to why dopamine underactivity in the PFC leads to PPI disruption. The answer may lie in the nature of the functional midbrain–PFC–Acb connectivity. DA-containing neurons localized in the VTA project both to PFC and to Acb (3). There is evidence that DA in the PFC modulates subcortical DA function by exerting an inhibitory influence on either the PFC excitatory glutamate (GLU)-containing neurons or the interneurons controlling the GLU neurons (13,37,46). These GLU neurons in the PFC have been shown to project to a number

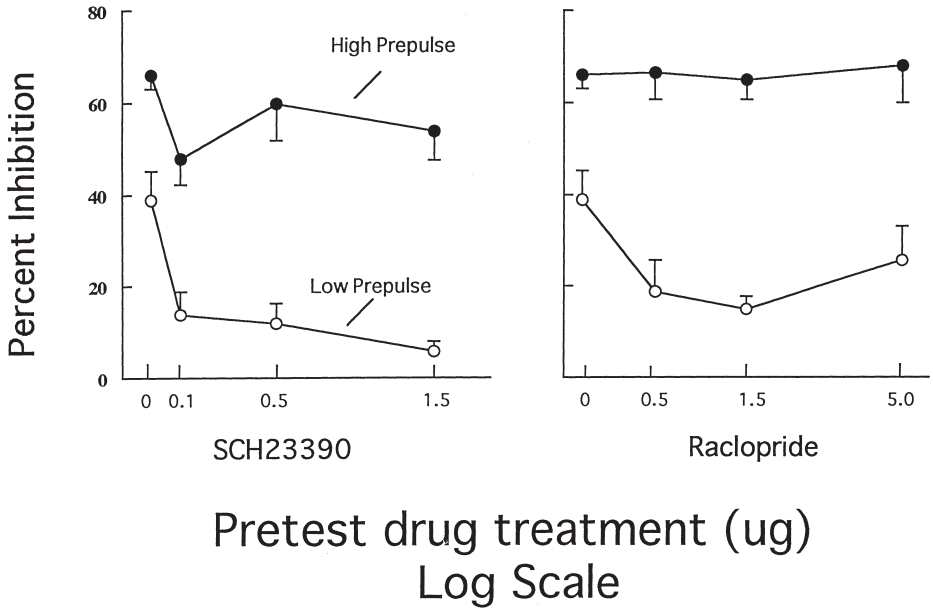

FIG. 2. Percent inhibition to the high and low prepulses for groups infused with SCH23390 (left panel) or raclopride (right panel).

of subcortical sites, including the Acb (38), and have also been reported to induce DA release in the Acb (1). Although GLU receptors have been shown to be localized on the presynaptic endings of the ascending DA fibers from the VTA to the Acb (53), more research is required to understand how descending GLU-containing projections modulate the regulation of DA release in subcortical sites. It seems clear that shutting off the DA system in PFC by destruction of PFC DA input or by local infusion of DA-specific antagonists may disinhibit the glutamatergic excitatory projection (32) and lead to overactivity of subcortical DA. Thus, decreased DA activity in the PFC leads to a disruption in PPI because of the consequent DA hyperactivity in the Acb. Further studies are required to assess this hypothesis.

The proposed PFC–Acb dopamine interaction mechanism is, nevertheless, consistent with other prefrontal PPI studies, whether these studies involved gross lesions or more specific infusions. First, ablating, NMDA, or ibotenic acid lesions of the PFC do not affect PPI [e.g., (19,28,45)]. This may be because the lesion has destroyed both the presynaptic DA terminals (inhibitory influence), and the postsynaptic cell body (excitatory influence). Thus, the removal of an inhibitory and an excitatory influence has no effect on DA activity in the Acb and, hence, no effect on PPI. Second, 6-OHDA lesions lead to PPI deficits (5,24). This effect is likely mediated by the destruction of the presynaptic DA terminals, so that there is no longer an inhibitory influence on the PFC excitatory GLU neurons. Thus, the PFC neurons, in their disinhibited state, have a greater than usual excitatory influence on the Acb, and hence, a disruption of PPI is observed. Third, infusion of DA antagonists into the PFC leads to blockage of the postsynaptic DA receptors on the excitatory neurons and has the same effect as 6-OHDA lesions, that is, disrupted PPI [this study, and (12)]. The paradoxical DA effects of cortical vs. subcortical manipulations have also been reported in behavioral studies of the effects of PFC DA on dopaminergic transmission in the basal ganglia (8,11,30,47). Several studies have shown that corticostriatal output neurons express both D_1 and D_2 receptor mRNA and binding sites (8,16,49). Does DA influence PFC output neurons by acting via D_1 or D_2 receptors? The present study, showing that intraPFC infusion of D_1-like and D_2-like antagonists reduces PPI, suggests that DA influences PFC output neurons by acting at both D_1- and D_2-like receptors. However, other behavioral studies suggest that the PFC DA action is D_1 specific (34,47). In contrast, electrophysiological findings indicate that DA inhibits the firing of PFC output neurons by acting at D_2-like receptors (37). It is clear that more research is needed to unravel these inconsistencies in the role of PFC DA.

The proposed PFC–Acb dopamine interaction mechanism is consistent with frontal lobe abnormalities found in schizophrenic patients [see, for review (17)]. For example, schizophrenic patients appear to have significantly smaller PFC volumes (29), reduced intraneuronal neuropil (36), and reduced regional cerebral blood flow in the dorsolateral PFC during performance on tests sensitive to PFC function (52). Moreover, accumulating data support the notion that the atrophy and decreased function of the PFC in schizophrenia is associated with decreased activity in the cortical D_1-like receptor system, and this is the cause of the negative symptoms or cognitive deficits of schizophrenia (9).

In conclusion, the finding of the current study, that DA antagonists infused into the rat prefrontal cortex disrupts PPI, supports the notion that frontal dopaminergic underactivity leads to deficits in sensorimotor gating. Given the implications for the effective pharmacological treatment of schizophrenia, further research is required to determine the exact role of DA function in the PFC and Acb, and to test the proposed mechanisms underlying frontal lobe modulation of sensorimotor gating.

ACKNOWLEDGEMENTS

This research was supported in part by Australian Research Council Grants to Rick Richardson and Jacquelyn Cranney. We acknowledge the generous gift of the raclopride from Dr. P. Sachdev, Dr. Michael Kiernan's assistance in constructing Fig. 1, and the reviewers' many helpful comments.

REFERENCES

1. Arnt, J. L.: Hyperactivity following injection of a glutamate agonist and 6,7-ADTN into rat nucleus accumbens and its inhibition by THIP. Life Sci. 28:1597–1603; 1981.
2. Beckstead, R. M.: Convergent thalamic and mesencephalic projections to the anterior medial cortex in the rat. J. Comp. Neurol. 166:403–416; 1976.
3. Bjorklund, A.; Lindvall, O.: Dopamine-containing systems in the CNS. In: Bjorklund, A.; Hokfelt, T., eds. Handbook of chemical neuroanatomy, vol. 2. Amsterdam: Elsevier; 1984:55–122.
4. Braff, D.; Stone, C.; Callaway, E.; Geyer, M.; Glick, I.; Bali, L.: Prestimulus effects on human startle reflex in normals and schizophrenics. Psychopharmacology (Berlin) 15:339–343; 1978.
5. Bubser, M.; Koch, M.: Prepulse inhibition of the acoustic startle response of rats is reduced by 6-hydroxydopamine lesions of the medial prefrontal cortex. Psychopharmacology (Berlin) 113:487–492; 1994.
6. Carlson, J. N.; Visker, K. E.; Keller, R. W., Jr.; Glick, S. D.: Left and right 6-hydroxydopamine lesions of the medial prefrontal cortex differentially alter subcortical dopamine utilization and the behavioral response to stress. Brain Res. 711:1–9; 1996.
7. DeBruin, J. P. C.; VanOyen, H. G. M.; VandePoll, N.: Behavioral changes following lesions of the orbital prefrontal cortex in male rats. Behav. Brain Res. 10:209–232; 1983.
8. Deutch, A. Y.; Clark, W. A.; Roth, R. H.: Prefrontal cortical dopamine depletion enhances the responsiveness of mesolimbic dopamine neurons to stress. Brain Res. 521:311–315; 1990.
9. Deutch, A. Y.: The regulation of subcortical dopamine systems by the prefrontal cortex: Interactions of central dopamine systems and the pathogenesis of schizophrenia. J. Neural Transm. (Suppl.) 36:61–89; 1992.
10. Divac, I.; Bjorklund, A.; Lindvall, O.; Passingham, R. E.: Converging projections from the mediodorsal thalamic nucleus and mesencephalic dopaminergic neurons in the neocortex in three species. J. Comp. Neurol. 180:59–72; 1978.
11. Duvauchelle, C. L.; Levitin, M.; MacConell, L. A.; Lee, L. K.; Ettenberg, A.: Opposite effects of prefrontal cortex and nucleus accumbens infusions of flupenthixol on stimulant-induced locomotion and brain stimulation reward. Brain Res. 576:104–110; 1992.
12. Ellenbroek, B. A.; Budde, S.; Cools, A. R.: Prepulse inhibition and latent inhibition: The role of dopamine in the medial prefrontal cortex. Neuroscience 75:535–542; 1996.
13. Ferron, A.; Thierry, A. M.; Le Douarin, C.; Glowinski, J.: Inhibitory influence of the mesocortical dopaminergic system on spontaneous activity or excitatory response induced from the thalamic mediodorsal nucleus in the rat medial prefrontal cortex. Brain Res. 302:257–265; 1994.
14. Freedman, L. J.; Cassell, M. D.: Thalamic afferents of the rat

infralimbic and lateral agranular cortices. Brain Res. Bull. 26: 957–964; 1991.
15. Fuster, J. M.: Prefrontal cortex in motor control. In: Brooks, V., ed. Handbook of physiology—The nervous system, II. Baltimore: Williams & Wilkins; 1982:1149–1178.
16. Gaspar, P.; Bloch, B.; Le Moine C.: D1 and D2 receptor gene expression in the rat frontal cortex: Cellular localization in different classes of efferent neurons. Eur. J. Neurosci. 7:1050–1063; 1995.
17. Goldman-Rakic, P. S.; Selemon, L. D.: Functional and anatomical aspects of prefrontal pathology in schizophrenia. Schizophr. Bull. 23:437–458; 1997.
18. Graham, F.: The more or less startling effects of weak prestimulation. Psychopharmacology (Berlin) 12:238–248; 1975.
19. Hammond, G. R.: Frontal cortical lesions and prestimulus inhibition of the rat's acoustic startle reaction. Physiol. Psychol. 2:151–156; 1974.
20. Hoffman, H. S.; Ison, J. R.: Reflex modification in the domain of startle: 1. Some empirical findings and their implications for how the nervous system processes sensory input. Psychol. Rev. 2:175–189; 1980.
21. Ison, J. R.; Krauter, E. E.: Reflex-inhibiting stimuli and the refractory period of the acoustic startle reflex in the rat. J. Comp. Physiol. Psychol. 86:420–425; 1974.
22. Jaskiw, G. E.; Weinberger, D. R.: The prefrontal cortex–accumbens circuit: Who's in charge? Behav. Brain Sci. 10:217–218; 1987.
23. Kahn, R. S.; Davidson, M.: Dopamine in schizophrenia. In: Den Boer, I.; Westenberg, H. G. M.; van Praag, H. M., eds. Advances in the neurobiology of schizophrenia. London: John Wiley & Sons Ltd; 1995:205–220.
24. Koch, M.; Bubser, M.: Deficient sensorimotor gating after 6-OHDA lesion of the rat medial prefrontal cortex is reversed by haloperidol. Eur. J. Neurosci. 6:1837–1845; 1994.
25. Koch, M.; Schnitzler, H.-U.: The acoustic startle response in rats—Circuits mediating evocation, inhibition and potentiation. Behav. Brain Res. 89:35–49; 1997.
26. Kolb, B.: Functions of the frontal cortex of the rat: A comparative review. Brain Res. Rev. 8:65–98; 1984.
27. Krettek, J. E.; Price, J. L.: The cortical projections of the mediodorsal nucleus and adjacent thalamic nuclei in the rat. J. Comp. Neurol. 171:157–191; 1977.
28. Lacroix, L.; Broerse, L. N.; Weiner, I.; Feldon, J.: The effects of excitotoxic lesion of the medial prefrontal cortex on latent inhibition, food hoarding, elevated plus maze, active avoidance and locomotor activity in the rat. Neuroscience 82:431–442; 1998.
29. Maher, B. A.; Manschreck, T. C.; Woods, B. T.; Yurgelun-Todd, D. A.; Tsuang, M. T.: Frontal brain volume and context effects in short-term recall in schizophrenia. Biol. Psychiatry 37:144–150; 1995.
30. Mitchell, J. B.; Gratton, A.: Partial dopamine depletion of the prefrontal cortex leads to enhanced mesolimbic dopamine release elicited by repeated exposure to naturally reinforcing stimuli. J. Neurosci. 12:3609–3618; 1992.
31. Paxinos, G.; Watson, C.: The rat brain in stereotaxic coordinates, 4th ed. San Diego: Academic Press; 1998.
32. Pycock, C. J.; Kerwin, R. W.; Carter, C. J.: Effect of lesion of cortical dopamine terminals on subcortical dopamine receptors in rats. Nature 286:74–77; 1980.
33. Rose, J. E.; Woolsey, C. N.: The orbitofrontal cortex and its connections with the mediodorsal nucleus in rabbit, sheep and cat. Res. Publ. Assoc. Res. Nerv. Ment. Dis. 27:210–232; 1948.
34. Sawaguchi, T.; Goldman-Rakic, P. S.: The role of D1-dopamine receptor in working memory: Local injections of dopamine antagonists into the prefrontal cortex of rhesus monkeys performing an oculomotor delayed-response task. J. Neurophysiol. 71:515–528; 1994.
35. Seeman, P.; Van Tol, H. H. M.: Dopamine receptor pharmacology. Trends Pharmacol. Sci. 15:264–270; 1994.
36. Selemon, L. D.; Rajkowska, G.; Goldman-Rakic, P. S.: Abnormally high neuronal density in two widespread areas of the schizophrenic cortex. A morphometric analysis of prefrontal area 9 and occipital area 17. Arch. Gen. Psychiatry 52:805–818; 1995.
37. Sesack, S. R.; Bunney, B. S.: Pharmacological characterization of the receptors mediating electrophysiological responses to dopamine in the rat medial prefrontal cortex: A microiontophoretic study. J. Pharmacol. Exp. Ther. 248:1323–1333; 1989.
38. Sesack, S. R.; Deutch, A. Y.; Roth, R. H.; Bunney, B. S.: Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: An anterograde tract-tracing study with *Phaseolus vulgaris* leucoagglutinin. J. Comp. Neurol. 290: 213–242; 1989.
39. Swanson, L. W.: Brain maps: Structure of the rat brain. Amsterdam: Elsevier; 1992.
40. Swerdlow, N. R.; Braff, D. L.; Masten, V. L.; Geyer, M. L.: Schizophrenic-like sensorimotor gating abnormalities in rats following dopamine infusion into the nucleus accumbens. Psychopharmacology (Berlin) 101:414–420; 1990.
41. Swerdlow, N. R.; Braff, D. L.; Taaid, N.; Geyer, M. A.: Assessing the validity of an animal model of deficient sensorimotor gating in schizophrenic patients. Arch. Gen. Psychiatry 51:139–154; 1994.
42. Swerdlow, N. R.; Caine, S. B.; Geyer, M. A.: Regionally selective effects of intracerebral dopamine infusion on sensorimotor gating of the startle reflex in rats. Psychopharmacology (Berlin) 108: 189–195; 1992.
43. Swerdlow, N. R.; Caine, S. B.; Braff, D. L.; Geyer, M. A.: The neural substrates of sensorimotor gating of the startle reflex: A review of recent findings and their implications. J. Psychopharmacol. 6:176–190; 1992.
44. Swerdlow, N. R.; Mansbach, R. S.; Geyer, M. A.; Pulvirenti, L.; Koob, G. F.; Braff, D. L.: Amphetamine disruption of prepulse inhibition of acoustic startle is reversed by depletion of mesolimbic dopamine. Psychopharmacology (Berlin) 100:413–416; 1990.
45. Swerdlow, R. N.; Lipska, B. K.; Weinberger, D. R.; Braff, D. L.; Jaskiw, G. E.; Geyer, M. A.: Increased sensitivity to the sensoriomotor disruptive effects of apomorphine after lesions of medial prefrontal cortex or ventral hippocampus in adult rats. Psychopharmacology (Berlin) 122:27–34; 1995.
46. Thierry, A. M.; Le Douarin, C.; Penit, C.; Ferron, A.; Glowinski, J.: Variation in the ability of neuroleptics to block the inhibitory influence of dopaminergic neurons on the activity of cells in the rat prefrontal cortex. Brain Res. Bull. 16:155–160; 1986.
47. Vezina, P.; Blank, G.; Glowinski, J.; Tassin, J. P.: Opposed behavioural outputs of increased dopamine transmission in prefrontocortical and subcortical areas: a role for the cortical D1 dopamine receptor. Eur. J. Neurosci. 3:1001–1007; 1991.
48. Vincent, S. L.; Khan, Y.; Benes, F. M.: Cellular colocalization of dopamine D1 and D2 receptors in rat medial prefrontal cortex. Synapse 19:112–120; 1995.
49. Vincent, S. L.; Khan, Y.; Benes, F. M.: Cellular distribution of dopamine D1 and D2 receptors in the rat medial prefrontal cortex. J. Neurosci. 13:2551–2564; 1993.
50. Wan , F. J.; Geyer, M. A.; Swerdlow, N. R.: Accumbens D2 modulation of sensorimotor gating in rats: Assessing anatomical localization. Pharmacol. Biochem. Behavior 49:155–163; 1994.
51. Wan, F. J.; Swerdlow, N. R.: Intra-accumbens infusion of quinpirole impairs sensorimotor gating of acoustic startle in rats. Psychopharmacology (Berlin) 113:103–109; 1993.
52. Weinberger, D. R.; Berman, K. F.; Saddath, R.; Torrey, E. F.: Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: A magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins. Am. J. Psychiatry 149:890–987; 1992.
53. Zavitsanou, K.; Mitsacos, A.; Giompres, P.; Kouvelas, E. D.: Changes in [^{3}H]AMPA and [^{3}H]kainate binding in rat caudate-putamen and nucleus accumbens after 6-hydroxydopamine lesions of the medial forebrain bundle: An autoradiographic study. Brain Res. 731:132–140; 1996.