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Prepulse inhibition of the acoustic startle response of rats is reduced by 6-hydroxydopamine lesions of the medial prefrontal cortex

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Abstract. Prepulse inhibition (PPI) of the acoustic startle response (ASR) is impaired by dopamine (DA) overactivity in the nucleus accumbens and anteromedial striatum. Since there is evidence that DA in the medial prefrontal cortex exerts an inhibitory control on striatal DA systems, it was investigated whether depletion of prefrontal DA reduces PPI. Rats were tested for PPI both before and after injections (2×1 µl per side) of vehicle, a low (3.0 µg/µl) or a high (6.0 µg/µl) dose of 6-hydroxydopamine hydrobromide (6-OHDA) into the prefrontal cortex. Only the high dose of 6-OHDA, leading to an 87% depletion of prefrontal DA, impaired PPI. The ability of an acoustic prepulse (75 dB, 10 kHz) to reduce the response to a startle pulse (100 dB noise burst) was maintained in sham lesioned rats, but was significantly disturbed in rats lesioned with the high dose of 6-OHDA. The 6-OHDA treatment did not affect the ASR amplitude in the absence of a prepulse. The reduction of PPI in lesioned rats correlated with the extent of DA depletion. These results suggest that the DA innervation of the prefrontal cortex is involved in the modulation of the ASR and they provide further evidence for opposite actions of prefrontal and subcortical DA systems in the control of behaviour. The present findings are discussed with regard to the potential role of prefrontal DA in schizophrenia.

Key words: Prefrontal cortex – Dopamine – Acoustic startle response – Prepulse inhibition – 6-Hydroxydopamine – Rat – Schizophrenia

The amplitude of the acoustic startle response (ASR) is reduced if a weak, non-startling stimulus is presented some 100 ms before the startle eliciting pulse occurs, an effect termed prepulse inhibition (PPI) (Hoffman and Ison 1980). PPI is thought to represent a centrally active inhibitory, or "gating" mechanism which can be activated by stimuli of several sensory modalities. Since PPI of the ASR was found to be impaired in certain neuropsychiatric disorders such as schizophrenia, there has been considerable interest in determining the neural and neurochemical substrates of this phenomenon of sensorimotor gating. Hence, a good deal of information is already available on the pharmacology and the neuroanatomy of PPI, mainly due to the work of Swerdlow and co-workers (summarized in Swerdlow et al. 1992a). It is evident from a series of experiments with rats that overactivity of the mesolimbic dopamine (DA) system, involving D_2 receptors in the nucleus accumbens (NAC), leads to a disruption of PPI. In rats with supersensitive DA receptors in the NAC, PPI is reduced by a low dose of apomorphine that does not affect PPI in intact rats (Swerdlow et al. 1986) and local infusion of DA into the NAC also reduces PPI (Swerdlow et al. 1990). Increased DA function of the anteromedial striatum also inhibits PPI (Swerdlow et al. 1992b).

Since DA systems innervating the forebrain form networks that mutually influence each other (Le Moal and Simon 1991), dopaminergic structures other than the NAC and the anteromedial striatum may also be involved in PPI. One such candidate is the medial prefrontal cortex (PFC) which receives input from the mesocortical DA system (Berger et al. 1976; Björklund and Lindvall 1984) and sends efferents to the NAC, the anteromedial striatum and to midbrain DA cell groups (Leonard 1969; Beckstead 1979; Sesack and Pickel 1992). The mode of interaction of cortical and subcortical DA systems has recently been investigated. As Jaskiw and Weinberger (1987) have pointed out, the DA innervation of the PFC may control the activity of subcortical structures. Evidence for this view derives from neurochemical studies where it was demonstrated that DA agonists locally injected into the PFC reduce in vivo DA metabolism in the NAC and the anterior striatum (Louilot et al. 1989; Jaskiw et al. 1991). In a behavioural study, local infusion of the DA-releasing agent amphetamine into the prefrontal cortex reduced locomotion that had been induced by amphetamine injection into the NAC (Vezina et al. 1991). The control of

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striatal DA activity by the PFC is also one of the main elements of recent hypotheses on the neural mechanisms underlying some schizophrenic symptoms (Robbins 1990; Grace 1991; Kerwin 1992). The neurophysiological mechanisms of this interaction between PFC and NAC are not yet precisely known. The underlying circuitry might include a glutamatergic excitatory projection from the PFC to the NAC and ventral tegmental area (Sesack et al. 1989; Sesack and Pickel 1992). Since DA mainly inhibits PFC neurons (Ferron et al. 1984; Peterson et al. 1987; Sesack and Bunney 1989), the destruction of prefrontocortical DA input would disinhibit this excitatory projection to the mesolimbic DA system. An increase in DA activity in the NAC (with increased D_2 receptor levels) following a lesion of prefrontal DA terminals has already been described (Pycock et al. 1980). According to this model, cortical DA depletion should have effects on PPI that are similar to the ones produced by increasing DA activity in the NAC and anteromedial striatum. In the present study this hypothesis was tested by investigating the effects of 6-hydroxydopamine (6-OHDA) lesion of the medial prefrontal cortex of the rat on PPI of the ASR.

Materials and methods

Subjects. Male Sprague-Dawley rats (Interfauna, Tuttlingen) weighing 220–290 g at the time of surgery were housed in groups of five or six animals and maintained on a 12:12 h light/dark schedule (lights on at 06:00 hours). They received 12 g rat chow/animal per day and tap water ad libitum.

Behavioural testing. All rats were tested for their ASR amplitude and PPI preoperatively, and were then divided into three groups with nearly similar mean startle amplitudes. This matching procedure was used to reduce the variability between the ASR amplitudes among the different groups. After surgery (see below) the rats were allowed 1 week to recover and were then tested again for their ASR amplitudes and PPI. The measurement of the ASR was accomplished after placing the rat in a wire mesh cage ($19.5 \times 9 \times 8$ cm) mounted on a digital balance (Sartorius L2200 S) inside a sound-attenuated chamber ($100 \times 80 \times 60$ cm). The deflections of the balance caused by the rats' movements were digitized and fed into a computer for further analysis. Following a 5-min acclimation period, during which time the rats received no stimuli except for a continuous white background noise of 55 dB SPL RMS, the tests began. The test session included an initial startle stimulus followed by four different trial types: pulse alone, prepulse followed by a pulse 100 ms after prepulse-onset, prepulse alone, and no stimulus. A total of 15 presentations of each trial type was given in a pseudorandom order. Interstimulus interval was 30 s. Acoustic stimuli (pulse: 100 dB SPL broad band noise bursts, 20 ms duration; prepulse: 75 dB SPL 10 kHz tone pulse, 0.4 ms rise/fall times, 20 ms duration) were delivered through loudspeakers at a distance of 40 cm from the test cage. The intensity of the prepulse was 10 dB below the startle threshold (Pilz et al. 1987). The whole-body startle amplitude was calculated from the difference between the highest peak-to-peak amplitudes of the output of the balance within time-windows of 80 ms after and 80 ms before the onset of the acoustic startle stimulus (pulse). The mean startle amplitude was calculated from the 15 values obtained for each trial block and the absolute change in ASR amplitude following prepulse was calculated. %PPI was calculated as [100 × (startle amplitude on prepulse trials − startle amplitude on pulse alone trials)/startle amplitude on pulse alone trials]. The response to the single startle pulse at the beginning of the test session was discarded.

Surgery. Ten minutes before anaesthesia was induced by an intraperitoneal injection of 7% chloral hydrate (0.5 ml/100 g), rats were intraperitoneally injected with 15 mg/kg desipramine (Serva, Heidelberg) in order to protect noradrenergic terminals from 6-hydroxydopamine toxicity (Breese and Traylor 1971). Rats were then placed into a Kopf stereotaxic apparatus with atraumatic earbars with the incisor bar set 3.3 mm below the interaural line. Following an incision of the scalp, burr holes were drilled over the injection sites and a blunted injection cannula, that was connected via polythene tubing to a 100 µl microsyringe (Exmire, Bischof, Leonberg), was slowly lowered to the respective injection sites. A microinfusion pump (CMA, Semrau, Sprockhövel) was used for intracerebral injections at the following coordinates: AP + 3.0 mm (bregma), L ± 0.8 mm, V 3.5 mm and 4.5 mm below bregma (Paxinos and Watson 1986). At each injection site 1.0 µl of the following solutions was infused over a period of 4 min. Controls received vehicle (0.9% saline containing 0.1 mg/ml ascorbic acid). Rats in the lesion groups were infused with 6-OHDA hydrobromide (Sigma, Deisenhofen) that was freshly dissolved in ice-cold vehicle at concentrations of either 3.0 µg/µl (6-OHDA_{low}) or 6.0 µg/µl (6-OHDA_{high}). In order to allow for diffusion of 6-OHDA, the cannula was left in place for 1 min after the infusion. Finally, the burr holes were closed with bone wax and the skin was sutured. Immediately after surgery, all rats were injected subcutaneously with 2×0.1 ml atropine sulfate (1 mg/ml).

Neurochemistry. One week after postoperative testing, rats were killed by decapitation, their brains were rapidly removed, cooled in ice-cold saline and sectioned in a cutting block (Heffner et al. 1980). Prefrontal cortex, nucleus accumbens, anterior and posterior striatum were dissected, weighed and stored in liquid nitrogen as described previously (Bubser et al. 1992). Frozen tissue samples were homogenized with a motor-driven pestle in HPLC mobile phase containing dihydroxybenzylamine (DHBA) as internal standard. Following centrifugation of tissue homogenates, the supernatant was filtered through a teflon syringe filter and 25 µl of the filtrate was injected into the HPLC system via a 50 µl sample loop. Compounds were separated on a reversed phase column (3.0 mm × 125 mm) with Nucleosil 5-C18 (Bischof, Leonberg) as stationary phase, that was preceded by a guard column (2 mm × 20 mm) filled with the same material. Biogenic amines were analyzed by an ESA 5100A electrochemical detector (Bischof, Leonberg) with the 5011 analytical cell in the screen mode (electrode 1: E = 0.00 V; electrode 2: E = + 0.32 V). The mobile phase (pH 4.50, flow rate 0.8 ml/min) consisted of a citrate/acetate buffer that contained octanesulfonic acid (35 mg/l) and 7% methanol. A more detailed description of the analytical procedures is given elsewhere (Bubser et al. 1992). Retention (min) of the compounds of interest were: DHBA (2.93), dihydroxyphenylacetic acid [DOPAC (3.72)], DA (4.28), 5-hydroxyindoleacetic acid [5-HIAA (8.20)], homovanillic acid [HVA (9.20)] and serotonin [5-HT (11.52)]. Noradrenaline (NA) could not be quantified, since it co-eluted with a large peak produced by an unidentified sample component. Chromatographic data were analyzed using the Axxiom 727 chromatography software (Sykam, Gilching).

Statistics. All data are presented as means ± SEM. Preoperative (PRE) and postoperative (POST) behavioural responses (mean ASR amplitude, absolute change in ASR amplitude and %PPI) were analyzed by the Wilcoxon matched-pairs signed-rank test. Neurochemical data were analyzed by one-way analysis of variance (ANOVA) with treatment as factor which was followed by Tukey's *t*-test for individual comparisons. Correlations between behavioural and neurochemical parameters were calculated by linear regression analysis. For all statistical calculations the GB-STAT statistical package (Bilany, Düsseldorf) was used. A P-value ≤ 0.05 was considered to represent a significant difference.

Results

Neurochemistry

The results of the neurochemical investigations are presented in Table 1. One-way ANOVA revealed significant differences between experimental groups for DA ($F = 93.6$, df 2,26, $P < 0.0001$) and 5-HT ($F = 8.1$, df 2,26, $P < 0.005$) in the prefrontal cortex. Post-hoc comparisons using Tukey's t-test revealed that prefrontal DA and 5-HT were significantly reduced in both lesion groups [6-$OHDA_{low}$: DA ($t = 11.2$, $P < 0.01$), 5-HT ($t = 2.67$, $P < 0.05$); 6-$OHDA_{high}$: DA ($t = 12.4$, $P < 0.01$), 5-HT ($t = 3.94$, $P < 0.01$)] when compared to vehicle-treated rats. There were no significant differences in prefrontal neurochemistry between 6-$OHDA_{low}$ and 6-$OHDA_{high}$ groups. 6-OHDA lesion of the prefrontal cortex did not affect the tissue content of transmitters and their metabolites in the nucleus accumbens, the anterior striatum and the posterior striatum.

Behaviour

Mean ASR amplitudes on pulse alone trials as well as %PPI are presented in Fig. 1. Neither the ASR on pulse alone trials ($P = 0.95$) nor %PPI ($P = 0.81$) was changed by vehicle infusion. In the 6-$OHDA_{low}$ group, the ASR on the pulse alone trials ($P = 0.95$) and %PPI ($P = 0.17$) did not change postoperatively. Infusion of 6-$OHDA_{high}$ significantly decreased %PPI ($P = 0.0077$) but did not significantly decrease the ASR in the pulse alone condition ($P = 0.11$). Prepulses of 75 dB (10 kHz) did not elicit startle responses (prepulse alone trials). Since the use of percent values (%PPI) may confound statistical analysis (Davis 1988), the absolute difference between the startle response on pulse and prepulse trials was also calculated. This difference did not change in the vehicle group (PRE: 76 ± 14, POST: 76 ± 14, $P = 0.72$) and the 6-$OHDA_{low}$ group (PRE: 98 ± 16, POST: 86 ± 12, $P = 0.59$), but decreased in the 6-$OHDA_{high}$ group (PRE: 107 ± 12,

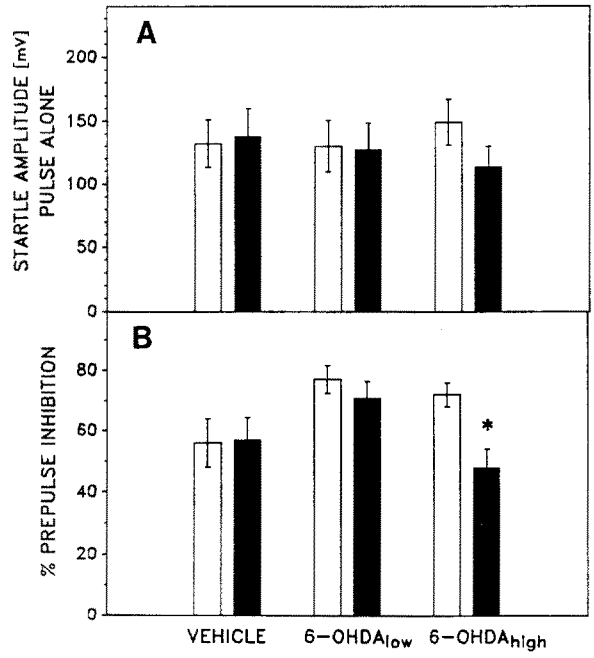

Fig. 1A, B. Effects of 6-OHDA lesion of the medial prefrontal cortex on the acoustic startle response on pulse alone trials (**A**) and on percent prepulse inhibition (**B**). The means ± SEM of vehicle ($n = 9$), 6-$OHDA_{low}$ ($n = 9$) and 6-$OHDA_{high}$ ($n = 9$) groups are presented for preoperative (□ PRE) and postoperative (■ POST) trials. *$P < 0.01$ (Wilcoxon matched-pairs signed-rank test)

Table 1. Effects of 6-OHDA lesion of the medial prefrontal cortex on tissue levels of biogenic amines and some of their metabolites in prefrontal cortex, nucleus accumbens, anterior and posterior striatum. Tissue levels (pg/mg wet weight) are means ± SEM (% control) of 9 animals/group

	DA		DOPAC		HVA		5-HT		5-HIAA	
Prefrontal cortex										
Vehicle	79.1 ± 5.8		30.4 ± 2.8		193 ± 22		487 ± 40		393 ± 30	
6-$OHDA^{a}_{low}$	16.6 ± 3.1[d]	(21)	24.6 ± 4.3	(81)	150 ± 20	(78)	317 ± 48[c]	(65)	376 ± 46	(96)
6-$OHDA^{b}_{high}$	10.1 ± 1.8[d]	(13)	38.9 ± 12.6	(128)	247 ± 63	(128)	236 ± 46[d]	(48)	317 ± 17	(81)
Nucleus accumbens										
Vehicle	7646 ± 531		1378 ± 88		730 ± 110		878 ± 74		682 ± 29	
6-$OHDA_{low}$	8157 ± 430	(107)	1499 ± 117	(109)	876 ± 81	(120)	989 ± 93	(113)	613 ± 17	(90)
6-$OHDA_{high}$	7688 ± 618	(101)	1462 ± 103	(106)	750 ± 116	(103)	915 ± 109	(104)	638 ± 31	(94)
Anterior striatum										
Vehicle	11547 ± 724		1352 ± 89		993 ± 104		329 ± 45		555 ± 65	
6-$OHDA_{low}$	12319 ± 474	(107)	1541 ± 84	(114)	878 ± 108	(88)	421 ± 51	(125)	522 ± 26	(94)
6-$OHDA_{high}$	11688 ± 407	(101)	1332 ± 58	(99)	860 ± 136	(87)	356 ± 15	(108)	509 ± 52	(92)
Posterior striatum										
Vehicle	7348 ± 264		952 ± 35		802 ± 134		740 ± 65		704 ± 52	
6-$OHDA_{low}$	7854 ± 864	(107)	1023 ± 121	(107)	629 ± 42	(78)	627 ± 64	(85)	613 ± 42	(87)
6-$OHDA_{high}$	8081 ± 595	(110)	1024 ± 63	(108)	752 ± 94	(94)	598 ± 45	(81)	663 ± 42	(94)

[a] 2 × 1.0 µl 6-OHDA HBr (3 µg/µl)/side
[b] 2 × 1.0 µl 6-OHDA HBr (6 µg/µl)/side
[c] $P < 0.05$
[d] $P < 0.01$ significantly different from vehicle group (ANOVA followed by Tukey's t-test)

Table 2. Correlation between behavioural and neurochemical parameters in vehicle controls ($n = 9$) and in rats with 6-OHDA lesions of the medial prefrontal cortex [6-$OHDA_{low}$ ($n = 9$) and 6-$OHDA_{high}$ ($n = 9$)]

Factors	Treatment	r	F	P
Pulse alone[c]	Vehicle	−0.45	1.79	0.22
vs	6-$OHDA^{a}_{low}$	0.08	0.04	0.84
DA	6-$OHDA^{b}_{high}$	0.09	0.05	0.83
% Prepulse inhibition[c]	Vehicle	−0.36	1.07	0.34
vs	6-$OHDA_{low}$	0.31	0.75	0.41
DA	6-$OHDA_{high}$	0.81	19.54	0.0079
Pulse alone	Vehicle	0.19	0.27	0.62
vs	6-$OHDA_{low}$	−0.21	0.31	0.59
5-HT	6-$OHDA_{high}$	0.31	0.72	0.42
% Prepulse inhibition	Vehicle	0.20	0.30	0.60
vs	6-$OHDA_{low}$	0.14	0.15	0.71
5-HT	6-$OHDA_{high}$	0.17	1.47	0.26

[a] 2 × 1.0 µl 6-OHDA HBr (3 µg/µl)/side
[b] 2 × 1.0 µl 6-OHDA HBr (6 µg/µl)/side
[c] Behavioural data are postoperative-preoperative differences in the startle response on pulse alone trials and in % prepulse inhibition

POST: 55 ± 8, $P = 0.0077$). The startle response on pulse alone trials did not decrease with time during the test sessions. This lack of short-term habituation was detected in all experimental groups (pre- and postoperatively) using an analysis by blocks of five trials.

Except for the reduction of %PPI which correlated significantly with the DA content of the prefrontal cortex of the 6-$OHDA_{high}$ group, there were no significant correlations between the behavioural parameters mentioned above and brain neurochemistry of experimental groups (Table 2). Since there was a gross overlap between the content of DA and also 5-HT in the prefrontal cortex of 6-$OHDA_{low}$ and 6-$OHDA_{high}$ groups, the correlation between cortical neurotransmitter content and behavioural parameters was also calculated for the combined lesion groups. Again, prefrontal DA content correlated only with the lesion-induced reduction of %PPI (Fig. 2).

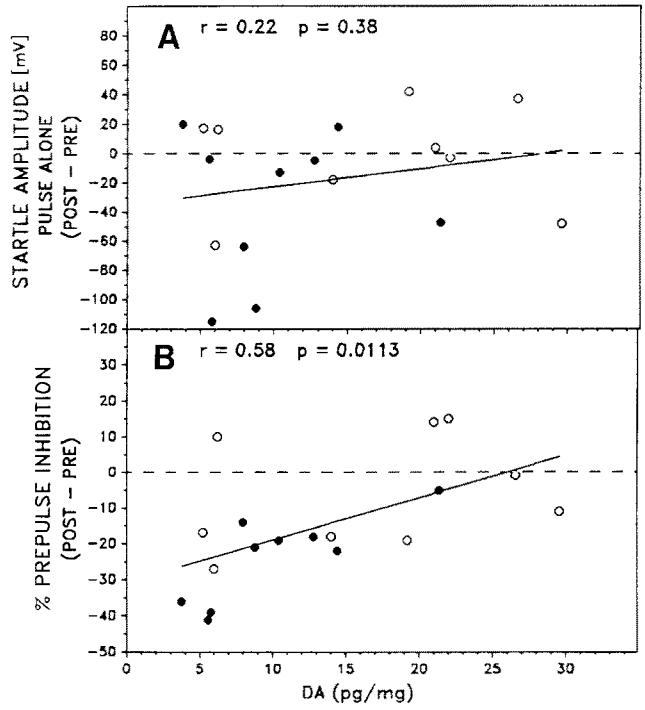

Fig. 2A,B. Correlation between behavioural changes (differences between postoperative and preoperative testing) and DA content in the medial prefrontal cortex of rats with prefrontal 6-OHDA lesions. **A** Acoustic startle response on pulse alone trials and **B** percent prepulse inhibition. Data of (○) 6-$OHDA_{low}$ ($n = 9$) and (●) 6-$OHDA_{high}$ ($n = 9$) groups are shown in different symbols to illustrate the variability of transmitter depletion. The *solid straight line* represents the curve obtained by linear regression analysis including data from all lesioned rats ($n = 18$)

Discussion

In the present study, infusion of 6-OHDA into the medial prefrontal cortex of rats decreased DA and 5-HT in the lesioned area and led to a reduction of PPI, without significantly affecting the ASR amplitude in pulse alone trials.

In accordance with previous studies (Oades et al. 1986; Swerdlow et al. 1986; Deutch et al. 1990), 6-OHDA produced a marked depletion of prefrontal DA. Lesion-induced depletion of tissue DA (79 and 87% in 6-$OHDA_{low}$ and 6-$OHDA_{high}$ groups, respectively) was in a range where compensatory changes in surviving neurons are no longer able to restore normal extracellular DA concentrations (Bean and Roth 1991). Thus, prefrontal DA function was most probably compromised in lesioned rats. The toxic actions of 6-OHDA were not confined to DA terminals, but the extent of prefrontal 5-HT depletion was smaller than DA depletion, as has been shown previously (Clarke et al. 1988; Jones and Robbins 1992). Since the high dose of 6-OHDA used in the present study is known to reduce cortical NA by 60–70% even in desipramine-pretreated rats (Bubser 1992), NA was most likely depleted in the present study. However, the HPLC assay did not allow for the neurochemical verification of this assumption. In subcortical structures, neither DA and 5-HT nor their metabolites were changed by prefrontal 6-OHDA lesion, which is in accordance with most other studies (Joyce et al. 1983; Koob et al. 1984; Jones and Robbins 1992). This lack of neurochemical changes in the basal ganglia indicates that the neurotoxic effects of 6-OHDA were confined to the PFC.

In the 6-$OHDA_{low}$ group which was less severely depleted of cortical transmitters than the 6-$OHDA_{high}$ group, PPI was not markedly impaired. The postoperative change in PPI in lesioned rats (6-$OHDA_{low}$ and 6-$OHDA_{high}$) correlated with the residual DA content in the prefrontal cortex. Since there was no significant correlation between behavioural changes and prefrontal 5-HT, it is suggested that the impairment of PPI reported here is due to reduced DA function in the PFC. However, an involvement of NA depletion in the lesion-induced deficit in PPI cannot be excluded. Whereas NA itself is not involved in PPI (Davis 1988), it might be conjectured that a combined reduction of prefrontal DA and NA contributed to deficient PPI. While there are no data concerning this issue available in the startle literature, data on other

behavioural parameters, e.g. locomotion, hint on the controversial nature of this issue. One point favouring the hypothesis of combined DA and NA depletion derives from the finding of Carter and Pycock, who showed that only a depletion of DA and NA within the prefrontal cortex increases locomotor activity whereas a selective reduction of NA alone does not (Carter and Pycock 1980). In contrast to this study, others have shown that the behavioural effects of a lesion of the ventral tegmental area, the source of the dopaminergic innervation of the prefrontal cortex, are antagonized by a lesion of the dorsal noradrenergic bundle (Taghzouti et al. 1988). Because of such conflicting results this issue cannot be satisfactorily solved at present. It can only be suggested that a combined depletion of both catechols may also contribute to the behavioural effects of prefrontal 6-OHDA lesion.

To the authors' knowledge, this is the first study demonstrating an involvement of prefrontal DA (and possibly NA) in PPI. Although based on a different methodology (using different stimulus parameters, strains, etc.), this finding is compatible with those of Swerdlow's group who already demonstrated that increased activity of cortical DA systems – produced by either infusing DA locally into the orbital cortex or by stimulation of supersensitive DA receptors in the prefrontal cortex – does not reduce prepulse inhibition (Swerdlow et al. 1986, 1992b). Thus, the action of prefrontal DA on PPI is opposite to that of DA in the NAC and anteromedial striatum, where increased DA function reduces PPI (Swerdlow et al. 1992a). It is interesting to note that the reduction of PPI observed after prefrontal 6-OHDA lesion and after infusion of DA into the NAC (Swerdlow et al. 1990, 1992a) is about the same. Our data are also compatible with the finding that aspiration lesions of the PFC do not impair PPI (Hammond 1974), because these lesions destroy both nerve cell bodies and fibres, thereby affecting both input to and output from the PFC. There is evidence that the destruction of DA terminals in the PFC disinhibits glutamatergic neurons of the PFC (Sesack and Bunney 1989) which, in turn, increase the DA activity in the NAC (Pycock et al. 1980). The mechanisms underlying the interaction between the PFC and the NAC are not yet fully elucidated. It has been proposed that a direct glutamatergic projection from the PFC terminates on the presynaptic side of the VTA-NAC projection, thereby increasing DA release in the NAC (Romo et al. 1986; Youngren et al. 1993). However, axo-axonic contacts between PFC efferents and VTA efferents terminating on NAC neurons have not been shown anatomically (Sesack and Pickel 1992). Thus, alternatively (or additionally), the effect could be mediated indirectly by glutamatergic efferents from the PFC to the VTA (Sesack and Pickel 1992), where stimulation of VTA neurons would also increase DA release in the NAC.

Deficient sensorimotor gating in the form of a reduced PPI has been repeatedly found in schizophrenic patients (Braff et al. 1978). This phenomenon has been attributed to deficits in a complex neuronal circuitry comprising an increased DA activity in subcortical structures, specifically in the NAC (Geyer et al. 1990; Caine et al. 1992; Swerdlow et al. 1992a). However, some authors have also linked schizophrenia with a hypofunctional DA system in the PFC (Jaskiw and Weinberger 1987; Tassin 1987; for reviews see Glowinski et al. 1984; Robbins 1990; Kerwin 1992). The most parsimonious statement would be that a combination of cortical and striatal disturbances could account for some symptoms of schizophrenia. Our data support the assumption that a DA (and possibly NA) hypofunction in the PFC is involved in the sensorimotor gating deficits observed in schizophrenics.

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