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Dopamine Autoreceptors in Rat Nucleus Accumbens Modulate Prepulse Inhibition of Acoustic Startle

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YAMADA, S., M. HARANO AND M. TANAKA. *Dopamine autoreceptors in rat nucleus accumbens modulate prepulse inhibition of acoustic startle*. PHARMACOL BIOCHEM BEHAV **60**(4) 803–808, 1998.—Dopamine and 3,4-dihydroxy phenylacetic acid (DOPAC) levels in discrete regions and apomorphine- or (−)-sulpiride–induced changes in electrically evoked dopamine release from nucleus accumbens slices were assessed after testing prepulse inhibition of acoustic startle (PPI) in rats. Dopamine and DOPAC levels in the nucleus accumbens, but not in the striatum, correlated well with PPI ($r = -0.64$ for dopamine, $r = -0.48$ for DOPAC). Evoked dopamine release from the nucleus accumbens did not differ between the high-PPI (more than 60%) and the low-PPI (less than 40%) group. When slices were superfused with 1 μM apomorphine, the S2/S1 ratio in rats showing high PPI was 0.77 ± 0.02 (mean ± SEM, 66% of control), significantly smaller than in the low-PPI group (S2/S1 ratio = 0.97 ± 0.08, 94% of control, $p < 0.05$). Moreover, (−)-sulpiride–induced increase in evoked dopamine release from the nucleus accumbens in the high-PPI group was inclined to be greater than in the low-PPI group. The results suggest that PPI differences between individuals may reflect the sensitivity of release-modulating dopamine autoreceptors in the nucleus accumbens. © 1998 Elsevier Science Inc.

Prepulse inhibition Dopamine release Nucleus accumbens Dopamine autoreceptor

THE startle reaction to a strong acoustic stimulus is reduced by prior presentation of a weak stimulus (5). This reduction, termed prepulse inhibition (PPI), has been used as a measure of sensorimotor gating and is significantly diminished in schizophrenic patients (2). In animal studies, PPI is changed by manipulations of neural circuitry linking the limbic cortex, striatum, pallidum, and pontine reticular formation (8,9,15). In particular, PPI is disrupted by systemic apomorphine or microinjection of apomorphine into the nucleus accumbens. The disruption of PPI by apomorphine is reversed by administration of a D_2 antagonist but not by D_1 antagonists, with potency correlating well with clinically effective dosages of each drug. Thus, disruption of PPI is a valid animal model for some aspects of schizophrenia (14,17). Substantial evidence supports the importance of dopaminergic activity in the nucleus accumbens in regulating PPI (13), although the precise mechanism underlying this regulation remains unclear.

The sensitivity of release-modulating dopamine autoreceptors in dopamine nerve terminals has been assessed by measuring agonist- or antagonist-induced changes in electrically evoked dopamine release from slices of nucleus accumbens or striatum in vitro (4,12,19,22). To clarify the regulation of PPI by the dopaminergic system in rat nucleus accumbens, PPI was assessed individual rats followed by measurement of dopamine and 3,4-dihydroxyphenyl acetic acid (DOPAC) levels in the nucleus accumbens, striatum and prefrontal cortex or by measurement of apomorphine- or (−)-sulpiride-induced changes in evoked dopamine release from nucleus accumbens slices.

METHOD

PPI Experiments

Male Wistar rats (350–400 g, $n = 18$) were housed in a light-, humidity-, and temperature-controlled environment maintained on a 12 L:12 D schedule (lights on at 0700 h) with food and water provided ad lib. Behavioral testing occurred between 0900 and 1500 h, during the light phase. Two startle chambers (SR-LAB, San Diego Instruments, San Diego, CA) were housed in a sound-attenuated room with a 60-dB ambi-

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ent noise level, and each consisted of a Plexiglas cylinder 8.2 cm in diameter resting in a 12.5 × 22.5 cm Plexiglas frame within a ventilated enclosure. Acoustic noise bursts were presented and background noise via a Supertweeter speaker mounted 24 cm above the animal. Sound levels were measured and calibrated with a Quest sound level meter. A piezoelectric device mounted below the Plexiglas frame detected and transduced motion within the cylinder. Delivery of acoustic stimuli was controlled by an SR-LAB microcomputer and interface assembly (San Diego Instruments) that rectified and digitized (from 0 to 4095) stabilimeter readings, and then recorded them. The readings were collected for 1 ms, beginning at stimulus onset. Scale–response sensitivities were calibrated using a SR-LAB startle calibration system. Each startle session began with 5-min acclimation period in the chamber to 68-dB background noise. After acclimation period, rats were exposed to two stimulus types presented in pseudorandom order: a 120-dB 40-ms noise burst (P); or P followed 100 ms after a 20-ms noise burst 8 dB above background (pP), for a total of 36 trials. Startle amplitude for each type of stimulus was defined as the mean maximum value of trials measured in arbitrary units. Percentage PPI was defined as 100 − [(startle amplitude on pP trials/startle amplitude on P trials) × 100]. PPI testing was performed on 2 consecutive days.

Dopamine and DOPAC Levels

After behavioral testing, rats were immediately decapitated and the brain was removed. The striatum, nucleus accumbens, and prefrontal cortex were dissected and stored at −80°C until biochemical analysis. Regional dopamine and DOPAC levels were measured by high-performance liquid chromatography with electrochemical detection (HPLC-ECD; ECD-100, Eicom, Kyoto, Japan) as previously reported (23). Tissue protein was measured by the Bio-Rad Protein assay (Bio-Rad, Richmond, CA). Data were expressed as nanograms of dopamine or DOPAC per mg protein.

Dopamine Release From Nucleus Accumbens Slices

In another experiment, 2 days after PPI testing on 2 consecutive days in 60 rats, the 20 animals showing highest PPI (high-PPI group) and 20 animals with the lowest PPI (low-PPI group) were selected. Averaging the 2 days, PPI was over 60% in the high-PPI group and under 40% in the low group. After decapitation the brains were rapidly removed and two slices, each 0.3-mm thick, were made with a Micro Slicer (Dohan EM, Kyoto, Japan) in ice-cold Krebs solution, aerated with 95% O_2 and 5% CO_2 at 1.0 and 1.7 mm anterior to the bregma, according to the atlas of Paxinos and Watson (10) (Fig. 1). Nucleus accumbens tissue in the slices was punched out using a metal tube (2 mm in inner diameter), resulting in four nucleus accumbens slices per animal. Two of these slices were superfused with Krebs solution containing different concentrations of drug in one experiment, and the other two slices were superfused with Krebs solution with no drug as controls. Composition of the Krebs solution (in mM) was: NaCl 118.0; KCl 4.9; $NaHCO_3$ 25.0; NaH_2PO_4 1.25; $CaCl_2$ 1.25; $MgCl_2$ 1.18; and glucose 11.0, together with nomifensine (3 μM). One slice in each of these pairs was placed in a chamber made from a Teflon tube in which platinum electrodes were mounted for electrical stimulation of the tissue. Four slices from a high PPI rat and four slices from a low PPI rat were superfused simultaneously. As the eight chambers were superfused with Krebs solution at 37°C. They also were aerated with 95% O_2 and 5% CO_2 at a flow rate of 0.7 ml/min.

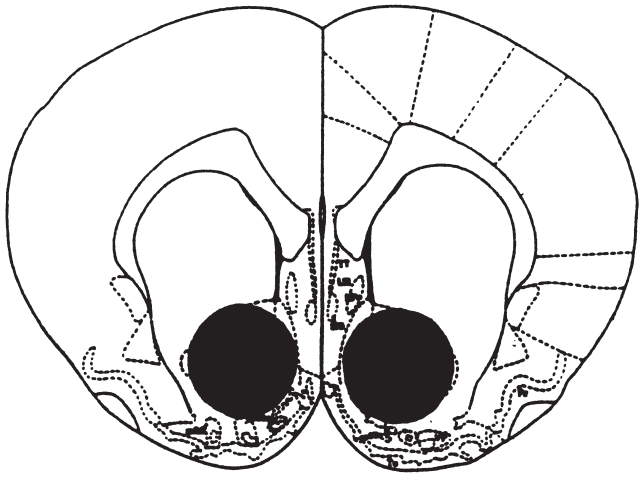

FIG. 1. Diagrammatic localization of the slice of the nucleus accumbens used for superfusion experiments.

Following superfusion with control Krebs solution for 37 min, the slices were simultaneously stimulated by trains of electrical pulses (1 Hz, 2 ms, 20 mA) for 2 min (S1) then the slices were superfused for 30 min either with control Krebs solution (four chambers) or with Krebs solution containing various concentrations (0.2, 1, or 10 μM) of apomorphine or (−)-sulpiride (four chambers for test). Effects of two of the three concentrations of a drug were examined in each experiment. An identical second stimulation (S2) was given at 22 min after the first. Overflowing superfusate was collected in a tube as 7-min fractions before and after each stimulation. Dopamine released into the superfusate was adsorbed on alumina, eluted with 300 μl of 0.1 M acetic acid, and quantified by HPLC-ECD by a method described previously (23). The evoked dopamine release during the S1 or S2 period was calculated as total release minus spontaneous release and designated S1 or S2, respectively. Spontaneous release during each stimulation was estimated from the sample collected during the 7-min period preceding stimulation. As the drug was presented in S2 but not in S1, the drug effect on evoked dopamine release was expressed as the S2/S1 ratio (mean ± SEM) or as a percentage of the control S2/S1 ratio (mean ± SEM) obtained from the chamber superfused with no drug throughout the experiment. Statistical comparisons were performed using one-way and two-way analyses of variance (ANOVA), followed by the Scheffe test.

TABLE 1

DA AND DOPAC LEVELS IN THREE BRAIN REGIONS*

	Prefrontal Cortex	Striatum	Nucleus Accumbens
DA	3.09 ± 0.27	229 ± 22	142 ± 11
DOPAC	1.26 ± 0.11	36.8 ± 4.1	36.8 ± 3.01
DOPAC/DA	0.42 ± 0.03	0.18 ± 0.02	0.3 ± 0.05

*Mean ng/mg protein ± SEM, $n = 18$. DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid.

TABLE 2
CORRELATION COEFFICIENT BETWEEN DOPAMINERGIC INDICES AND PPI OR STARTLE AMPLITUDE

	Frontal Cortex		Striatum		*N. Accumbens*	
	PPI	Amplitude	PPI	Amplitude	PPI	Amplitude
DA	−0.5*	0.31	−0.37	−0.21	−0.64†	0.05
DOPAC	−0.16	−0.21	−0.33	0.01	−0.48*	0.03
DOPAC/DA	0.35	−0.54*	0.15	0.18	0.08	−0.12

PPI, prepulse inhibition; DA, dopamine; DOPAC, 3,4-dihydroxyphenyl acetic acid. Pearson correlation, *$p < 0.05$, †$p < 0.01$, $n = 18$.

RESULTS

In the animals used for tissue amine measurements, the mean startle amplitude (arbitrary units) and PPI were 1545 ± 330 (mean ± SEM, $n = 18$) and 66% ± 4 (mean ± SEM, $n = 18$), respectively. Individual PPI was stable from day 1 to day 2 ($r = 0.86$, $n = 18$, $p < 0.001$). Dopamine and DOPAC levels in the regions sampled are shown in Table 1; correlations between dopaminergic indices and startle amplitude and/or PPI as shown in Table 2. Dopamine and DOPAC levels in the nucleus accumbens, but not the striatum, correlated negatively with the PPI ($r = -0.64$ for dopamine, $p < 0.01$ and $r = -0.48$ for DOPAC, $p < 0.05$). No correlation was found with startle amplitude. In the prefrontal cortex dopamine, but not DOPAC levels, correlated negatively with PPI ($r = -0.5$, $p < 0.05$) and DOPAC/dopamine ratios correlated negatively with startle amplitude ($r = -0.54$, $p < 0.05$).

For the animals used for the slice perfusion experiments, PPI in the high and low PPI groups was 75.5 ± 5.4% and 25.5 ± 5.6% (mean ± SEM, $n = 20$ per group), respectively. Evoked dopamine release from slices of nucleus accumbens was 0.33 ± 0.01 ng/fraction. No significant difference in evoked dopamine release was seen between high- and the low-PPI groups (Table 3). Apomorphine reduced evoked dopamine release in a concentration-dependent manner. When slices were superfused without apomorphine, S2/S1 was 1.08 ± 0.04 for the low-PPI group and 1.19 ± 0.05 for the high-PPI group (no significant difference). As shown in Table 3 and Fig. 2, the apomorphine-induced reduction in evoked dopamine release in the high-PPI group was greater than in the low-PPI group [two-way ANOVA, treatment, $F(1, 30) = 7.9$, $p < 0.01$; percent of control S2/S1 ratio, 96 ± 5.8% for the high-PPI group and 90 ± 7.6% for the low-PPI group with 0.2 μM apomorphine; 66 ± 4.3% for the high-PPI group and 94 ± 5.3% for the low-PPI group with 1 μM apomorphine; and 61 ± 5.5% for the high group and 63 ± 5.3% for the low group with 10 μM apomorphine]. At a concentration of 1 μM, apomorphine-induced reduction in evoked dopamine release for the high-PPI group was greater than for the low-PPI group [one-way ANOVA $F(5, 24) = 5.66$, $p = 0.0014$, Scheffe F test, $F = 3.7$ $p < 0.05$]. (−)-Sulpiride increased evoked dopamine release in a concentration-dependent manner. (−)-Sulpiride–induced increase in evoked dopamine release from the slices of the high-PPI group was greater than that from the low-PPI group but did not reach the significant difference [two-way

TABLE 3
EFFECTS OF APOMORPHINE ON EVOKED DOPAMINE RELEASE FROM STRIATAL SLICES IN LOW- AND HIGH-PPI RATS

	Conc.		DA Release (ng/Fraction)		
	μM	*n*	S1	S2	S2/S1 Ratio
Apomorphine	0 (S2)				
Low PPI		9	0.33 ± 0.02	0.36 ± 0.02	1.08 ± 0.04
High PPI		9	0.34 ± 0.03	0.38 ± 0.03	1.19 ± 0.05
Apomorphine	0.2 (S2)				
Low PPI		6	0.35 ± 0.03	0.33 ± 0.02	0.97 ± 0.04
High PPI		6	0.36 ± 0.03	0.38 ± 0.05	0.99 ± 0.10
Apomorphine	1 (S2)				
Low PPI		7	0.33 ± 0.05	0.30 ± 0.03	0.97 ± 0.08
High PPI		7	0.36 ± 0.04	0.27 ± 0.04†	0.77 ± 0.02*
Apomorphine	10 (S2)				
Low PPI		5	0.34 ± 0.04	0.23 ± 0.03†	0.78 ± 0.05
High PPI		5	0.30 ± 0.05	0.22 ± 0.03†	0.70 ± 0.04

PPI, prepulse inhibition; DA, dopamine; conc., concentration; S1, DA released by 1st stimulation; S2, DA released by 2nd stimulation. *$p < 0.05$, compared to low-PPI group; †$p < 0.05$, compared to control S2 value (no apomorphine) of each corresponding group, Scheffe *F*-test. Apomorphine-induced reduction of S2/S1 ratio in high-PPI group was significantly greater than that in low-PPI group [two-way ANOVA, treatment, $F(1, 30) = 7.9$, $p < 0.01$]

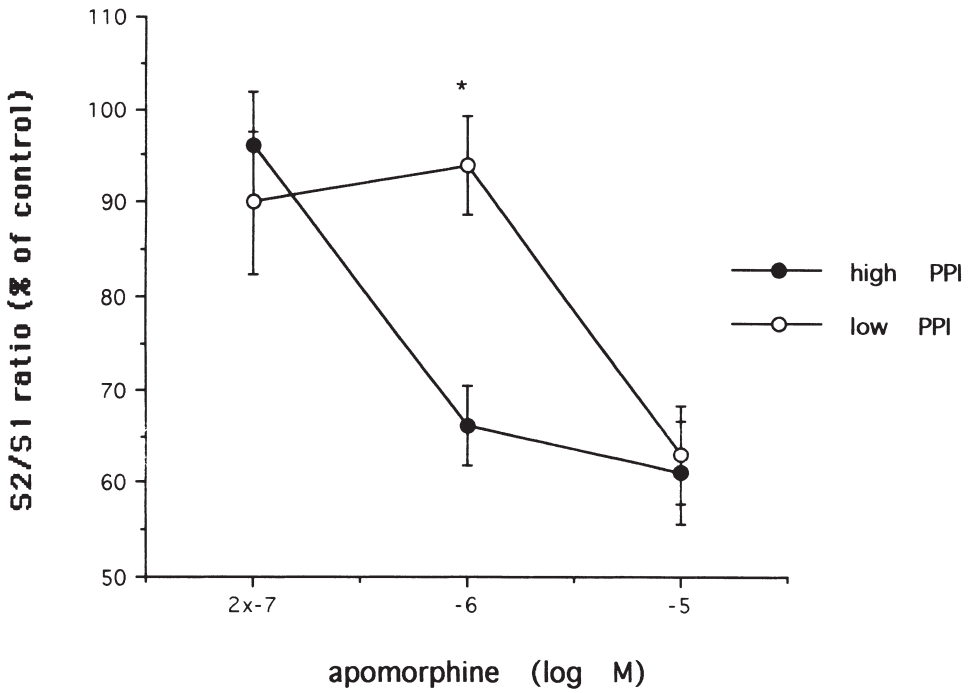

FIG. 2. Effects of apomorphine on evoked dopamine release from the nucleus accumbens in rat of low PPI group (○) and high PPI group (●). Data represents S2/S1 ratio (mean % ± SEM of drug-free control, $n = 5$ to 7 for each point, n representing number of animals. Two of four slices taken from one animal were superfused with different concentrations of apomorphine in one experiment; another two slices were superfused with Krebs solution without apomorphine as controls [two-way ANOVA, treatment, $F(1, 30) = 7.9$, $p < 0.01$]. Apomorphine reduced the evoked dopamine release from slices of nucleus accumbens [one-way ANOVA $F(5, 24) = 5.66$, $p = 0.0014$] $^*p < 0.05$, when compared with low PPI group (Scheffe test, $F = 3.93$).

ANOVA, treatment, $F(1, 36) = 3.28$, $p = 0.078$; percent of control S2/S1, 153 ± 2.2% of control for the high group and 143 ± 3.9% of control for the low group with 0.2 μM (−)-sulpiride; 221 ± 16.3% of control for the high group and 179 ± 12.8% of control for the low group with 1 μM (−)-sulpiride; and 273 ± 11% of control for the high group and 267 ± 13% of control for the low group with 10 μM (−)-sulpiride; Fig. 3].

DISCUSSION

Although interindividual PPI was variable, individual PPI was quite stable between 2 consecutive days, suggesting that the function of sensorimotor gating could be biologically defined in each rat. The magnitude of PPI was inversely related to dopamine and DOPAC levels in the nucleus accumbens, but not in the striatum: rats with largest PPI had the lowest dopamine levels. These results indicate that individual differences of dopaminergic activity in the nucleus accumbens have considerable influence on degree of PPI, which is in agreement with previous findings that a microinjection of apomorphine in the nucleus accumbens caused a significant reduction of PPI through the activation of postsynaptic dopamine receptors (14). Additionally, the PPI impairment from methamphetamine can be reversed by depletion of mesolimbic dopamine (13). Interference with PPI by apomorphine is not reversed by D_1 antagonists but is reversed by D_2 antagonists to a degree correlating with effective clinical doses of each drug (14). Individual PPI also correlated negatively with dopamine levels but not DOPAC levels in the prefrontal cortex, which may reflect a lack of release-modulating dopamine autoreceptors in the prefrontal cortex (11). DOPAC/dopamine ratios in the prefrontal cortex correlated negatively with startle amplitude. Thus, dopaminergic activity in the prefrontal cortex appears to inhibit startle amplitude. The result is consistent with the previous report that apomorphine increases startle amplitude in prefrontally lesioned rat but not sham-lesioned rat (15). A novel finding in the present study is that the reduction induced by 1 μM apomorphine in evoked dopamine release from the nucleus accumbens of the high PPI group were greater than in the low PPI group. Apomorphine reduces evoked dopamine release from the nerve terminals of dopaminergic neurons by activating release-modulating dopamine autoreceptors (4,12,20–22). We previously have reported that apomorphine-induced reduction in evoked dopamine release from striatal slices was decreased by the intermediate-term treatment with methamphetamine (19) and was increased by the chronic treatment with haloperidol (21). Thus, the magnitude of apomorphine-induced reduction in evoked dopamine release precisely reflects the sensitivity of dopamine autoreceptors. The present results indicate that the sensitivity of dopamine autoreceptors in the nucleus accumbens may affect PPI, low PPI being associated with low sensitivity of release-modulating dopamine autoreceptors. Dopamine release induced by a weak prepulse would activate dopamine autore-

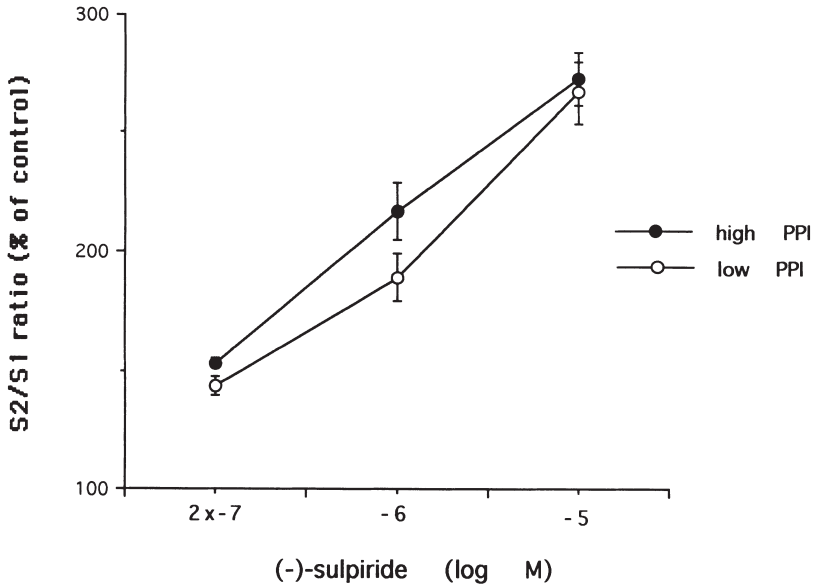

FIG. 3. Effects of (−)-sulpiride on evoked dopamine release from the nucleus accumbens in rat of low PPI group (○) and high PPI group (●). Data represents S2/S1 ratio (mean % ± SEM of drug free control, $n = 7$ for each point, n representing number of animals). No significant difference was found between the two groups [two-way ANOVA treatment, $F(1, 36) = 3.28, p = 0.078$].

ceptors that reduce dopamine release from dopaminergic nerve terminals, reducing the acoustic startle reflex. Recently, Humby et al. (6) have reported that during the presentation of startling stimuli, extracellular dopamine levels in the nucleus accumbens decrease from baseline quantities, a change that is inhibited by presentation of prepulse. The reduction of extracellular dopamine levels by startling stimuli could result from negative feedback inhibition of dopamine neurons. Dopamine release induced by a weak prepulse would activate dopamine autoreceptors, reducing dopamine release from dopamine nerve terminals and preventing further inhibition of dopaminergic neuronal activity via the accumbens–ventral tegmental feedback loop, resulting in attenuation of the reduction in extracellular dopamine level associated with P stimuli. (−)-Sulpiride–induced increase in evoked dopamine release from the nucleus accumbens in the high-PPI group was inclined to be greater than in the low-PPI group, which is not inconsistent with the data of apomorphine-induced reduction of evoked dopamine release, because the high response to (−)-sulpiride–induced increase in evoked dopamine reflects the high sensitivity of release modulating dopamine autoreceptors (20,21). PPI reportedly is also disrupted by administration of *N*-methyl-D-asparatate (NMDA) and/or non-NMDA antagonists (1,7,18). Further study is necessary to assess the influence of glutamatergic projections to the nucleus accumbens in the regulation of PPI (3,16).

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