Pergamon

Pharmacology Biochemistry and Behavior, Vol. 52, No. 4, pp. 649-654, 1995

0091-3057/95 $9.50 + .00

0091-3057(95)00160-3

Prepulse Inhibition of Acoustic Startle, a Measure of Sensorimotor Gating: Effects of Antipsychotics and Other Agents in Rats

CHRISTINA JOHANSSON,*[1] DAVID M. JACKSON,* JIANHUA ZHANG† AND LENNART SVENSSON†

*Department of Behavioural and Biochemical Pharmacology, Preclinical Research and Development, Astra Arcus AB, S-151 85 Södertälje, Sweden
†Department of Pharmacology, University of Göteborg, Göteborg, Sweden

Received 30 November 1994; Accepted 23 March 1995

JOHANSSON, C., D. M. JACKSON, J. ZHANG AND L. SVENSSON. *Prepulse inhibition of acoustic startle, a measure of sensorimotor gating: Effects of antipsychotics and other agents in rats.* PHARMACOL BIOCHEM BEHAV **52**(4) 649-654, 1995.—Schizophrenic patients are deficient in various neurologic measures reflecting information processing. One such measure is prepulse inhibition (PPI) of acoustic startle, in which schizophrenics display less inhibition than normal subjects. PPI is also diminished in rats treated with psychotomimetic drugs such as amphetamine and phencyclidine. PPI has been suggested as a model relevant for studying the pathophysiology of schizophrenia. We studied the effect of a variety of antipsychotics and putative antipsychotics and some key reference compounds on the acoustic startle response (ASR) and PPI. Some, but not all, antipsychotics tested (mainly selective dopamine D_2 antagonists) enhanced PPI. Remoxipride and clozapine, both of which are antipsychotics, and the very potent and highly selective D_2 antagonist, NCQ-298, did not. It is concluded that enhanced PPI in otherwise untreated rats does not reflect antipsychotic efficacy. We further noted that the effect on PPI was independent of the effect on ASR.

Prepulse inhibition Antipsychotics NMDA antagonists Dopamine Serotonin Rat

THE AIM of the present investigation was to study the effect of a number of psychotropic agents on the acoustic startle response (ASR) and prepulse inhibition (PPI) of this response. ASR is a sensorimotor response to a sudden acoustic stimulus. PPI is a phenomenon that appears when the acoustic stimulus causing the ASR is preceded by a weak prepulse 60-500 ms before the main pulse. This markedly diminishes the response (4). Techniques are available that make it possible to study PPI in a number of animal species, most importantly in humans and rats (8).

Several studies have demonstrated a decreased PPI in schizophrenia (5,9). Decreased PPI is also seen in psychosis-prone young adults (29), schizotypal personality disorder (6), obsessive compulsive disorder (31), Huntington's disease (35), and young children suffering from nocturnal enuresis (23).

A disruption of PPI similar to that seen in schizophrenics can also be induced in rats by the administration of dopamine (DA) receptor agonists such as apomorphine (33) and amphetamine or noncompetitive NMDA antagonists such as phencyclidine (PCP) (16).

The present study was performed to examine the effect of a variety of antipsychotics and putative antipsychotics, together with some key reference compounds, on ASR and PPI. The main objective of the study was to see whether there was a relationship between the effect of various substances in the acoustic startle model and their clinical efficacy.

METHODS

Animals

Male Sprague-Dawley rats (B&K Universal, Sollentuna, Sweden), weighing between 250 and 350 g, were used. The animals were housed on a 12 L : 12 D cycle with lights on at 0600 h. The temperature was 20 ± 1°C and the humidity 55 ± 5%. The animals were kept in groups of four in plastic cages. Food pellets and tapwater were available ad lib. Test-

[1] To whom requests for reprints should be addressed. Email: christina.johansson@arcus.se.astra.com

ing started 1 week after the arrival of the rats. The study was approved by the local ethical committee for animal research at Södra Roslags Tingsrätt, Stockholm.

Drugs

1-(1-phenylcyclohexyl)piperidine HCl (PCP), (5R,10S)-(+)-5-methyl-10,11-dihydro-5H-dibenzo(a,d)cyclohepten-5,10-imine hydrogen maleate [(+)MK-801, dizocilpine], (5S,10R)-(−)-5-methyl-10-11-dihydro-5H-dibenzo(a,d)cyclohepten-5,10-imine hydrogen maleate [(−)MK-801], R(+)-2-dipropylamino-8-hydroxy-1,2,3,4-tetrahydronaphthalene HBr [(+)8-OH-DPAT] and (±)-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane HBr [(±)DOB] (RBI, Natick, MA) were dissolved in saline. R(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine HCl [(+)SCH23390] and S(−)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine HCl [(−)SCH23388] (RBI) were dissolved in a few drops of propylene glycol and adjusted to volume with distilled water. Ketalar solution (Parke-Davis, Barcelona, Spain) contained (±)-2-(2-chlorophenyl)-2-(methylamino)cyclohexanone HCl (ketamine). (S)(+)-α-methylphenylethylamine sulfate (*d*-amphetamine) (Sigma, St. Louis, MO), 5,6,6-a,7-tetrahydro-6-methyl-4H-dibenzo(de,g)quinoline-10,11-diol HCl (apomorphine) (Sandoz, Basel, Switzerland), S(−)-3-bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2,6-dimethoxybenzamide HCl monohydrate (remoxipride), S(−)-3,5-dichloro-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2-hydroxy-6-methoxybenzamide (+)-tartrate (raclopride), R(+)-3-(3-hydroxyphenyl)-*N*-propylpiperidine hydrochloride [(+)3-PPP], S(−)-3-(3-hydroxyphenyl)-*N*-propylpiperidine hydrochloride [(−)3-PPP, preclamol], (S)-5,6-dimethoxy-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-3-iodo-salicylamide mesylate (NCQ-298), S(−)-5-fluoro-8-hydroxy-2-(dipropylamino)tetralin HCl [(−)-UH-301] (Astra Arcus, Södertälje, Sweden) were dissolved in saline. 4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone base (haloperidol) (Sigma) and 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo(b,e)(1,4)-diazepine base (clozapine) (Sandoz), 3-[2-(4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl)ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido(1,2-a)-pyrimidin-4-one base (risperidone) (Janssen Pharma, Beerse, Belgium), 6-[2-(4-[bis(4-fluorophenyl)methylene]-1-piperidinyl)-ethyl]-7-methyl-5H-thiazolo(3,2-a)pyrimidin-5-one base (ritanserin) (Janssen Pharma) and S(−)-3-bromo-*N*[(1-ethyl-2-pyrrolidinyl)methyl]-2-hydroxy-6-methoxybenzamide base) [(−)FLA-797] (Astra Arcus) were dissolved in a few drops of acetic acid diluted in distilled water, and the pH was adjusted to around 5 using NaOH. 8-[4-(4-[2-pyrimidinyl)-1-piperazinyl)butyl]-8-azaspiro(4.5)-decane-7,9-dione HCl (buspirone; Sigma) was dissolved in distilled water. All drugs were injected subcutaneously (SC) in a volume of 2 ml/kg.

Apparatus

The startle response was recorded by an MOPS 2b startle response recording system (Metod och Produkt Svenska AB, Göteborg, Sweden). The rat was placed in a small wire-mesh cage (18.5 × 7 × 6.5 cm) suspended from the ceiling of a sound-attenuated enclosure (52 × 42 × 38 cm). Four enclosures were used in parallel. The wire-mesh cage was connected by a piston to a moving coil transducer (with a sudden movement of the rat inside the cage causing a movement of the piston), the change in velocity of which was converted to an analogue signal by the transducer. This signal was sampled and digitised with a 12-bit digital resolution by a microcomputer which also served to control the delivery of acoustic stimuli. Startle amplitude was defined as the maximum signal amplitude (digital units) that occurred during the first 30 ms after delivery of the startle-eliciting stimulus. The acoustic signal consisted of white noise delivered to the rat by two high-frequency loudspeakers built into the ceiling of the sound-attenuated enclosure. A continuous acoustic signal provided a background white noise inside the enclosure of 62 dB(A). The background noise was interrupted at stimulus presentations by a 20-ms burst of white noise with a rise/decay time of < 1 ms. The cages were calibrated to ensure equal sensitivity before test, and rats tested at several occasions were always tested in the same cage.

Procedure

Each experiment was composed of at least four different doses of a particular drug including a vehicle control. The rats were tested every 3rd or 4th day in a crossover design, with all rats receiving all doses of the drug tested. On each test day, the animals were injected with drug immediately before (apomorphine) or 5 min (PCP, MK-801, ketamine, and 8-OH-DPAT), 20 min [amphetamine and (S)-UH-301] or 60 min (all other drugs) before putting them into the cages. They were then given a 10-min adaptation period inside the cage before the start of the first stimulus session. Each stimulus session consisted of 10 single or paired noise bursts. In the case of paired pulses, the prepulse (74 dB—i.e., 12 dB above background level) preceded the main pulse (105 dB) by 60 ms. The noise bursts were delivered 10 s apart, a time period that produced a minimum of habituation within the period. The time between sessions was 70 s. The number of sessions was always eight, in which the first session was discarded from the statistical analysis to further minimise within-period habituation. The session order was the following: 105 dB single pulse only, 74 dB single pulse, 74 dB prepulse + 105 dB main pulse, 105 dB single pulse, 74 dB prepulse + 105 dB main pulse, 105 dB single pulse, 74 dB prepulse + 105 dB main pulse, and 105 dB single pulse. In all, the duration of the procedure was 30 min. The first test day was a habituation/pretest following the experimental design given before with the exception that no drug was administered. The data from the first test day were discarded. Single pulses of 74 dB were not found to induce a recognisable startle response in any of the experiments.

Descriptive Statistics

The mean response amplitude in single-pulse stimulus conditions and paired-pulse conditions was calculated for each animal and treatment. These individual values were used in the statistical analysis as described subsequently.

The level of PPI was calculated using the formula: PPI = 100 − [(*PP*/*P*) × 100], where *PP* designates the averaged response to paired pulses and *P* the ASR (i.e., the response to single 105-dB pulses). Using this formula, a 0% value indicates no difference between the single-pulse and paired-pulse response (i.e., no PPI).

Statistical Analysis

Nonparametric statistics were used to control for possible deviations in the normal distribution of the data. The statistical tests were Friedman two-way analysis of variance by ranks followed by Wilcoxon *t*-test. Two-tailed levels of significance were used and $p > 0.05$ was considered nonsignificant.

RESULTS

Table 1 presents the results after sorting the different drugs into groups according to their putatively most important receptor interactions. The results of Friedman's tests are given within brackets in the text. No data were discarded between the analyses of ASR and PPI, and consequently, the degrees of freedom and numbers of animals were always the same within one drug treatment. The results of Wilcoxon *t*-tests are given in Table 1.

Glutamate Receptor Active Drugs

The noncompetitive NMDA antagonist, (+)MK-801, caused an increase in ASR amplitude at intermediate doses (Freedman's ANOVA: $\chi^2 = 17.5$; $df = 3$; $p = 0.0006$; $n = 11$). This property was shared by the two other noncompetitive NMDA antagonists tested, PCP ($\chi^2 = 17.9$; $df = 3$; $p = 0.0005$; $n = 23$), and, marginally, ketamine ($\chi^2 = 7.6$; $df = 3$; $p = 0.055$; $n = 12$). Higher doses of PCP and (+)MK-801 caused a diminished ASR. (−)MK-801, the less potent enantiomer of MK-801, did not affect ASR ($\chi^2 = 5.1$; $df = 3$; $p = 0.16$; $n = 12$). PCP ($\chi^2 = 41.5$; $p < 0.0001$), (+)MK-801 ($\chi^2 = 17.9$; $p = 0.0005$), (−)MK-801 ($\chi^2 = 21.1$; $p = 0.0001$), and ketamine ($\chi^2 = 18$; $p = 0.0004$) caused a dose-related disruption of PPI.

Dopamine Receptor Active Drugs

The nonselective DA receptor agonist, apomorphine ($\chi^2 = 12.4$; $df = 3$; $p = 0.0062$; $n = 15$), caused an increase in ASR amplitude, whereas the indirect DA receptor agonist, *d*-amphetamine ($\chi^2 = 2.44$; $df = 3$; $p = 0.49$; $n = 15$), failed to alter ASR. Both apomorphine ($\chi^2 = 15.1$; $p = 0.0017$) and amphetamine ($\chi^2 = 30$; $p < 0.0001$) caused a decrease in PPI. However, (−)3-PPP, which is a DA D_2 autoreceptor agonist and a postsynaptic DA D_2 antagonist, did not affect ASR or PPI ($\chi^2 = 2.4$; $df = 3$; $p = 0.5$; $n = 15$, and $\chi^2 = 4$; $p = 0.26$, respectively). The DA D_2 agonist and σ ligand, (+)3-PPP, caused a significant decrease in both behavioural measures (ASR: $\chi^2 = 11.4$; $df = 3$; $p = 0.0097$; $n = 15$; PPI: $\chi^2 = 21.3$; $p < 0.001$). The DA D_1 antagonist, SCH23390 (ASR: $\chi^2 = 1.5$; $df = 4$; $p = 0.82$; $n = 9$; PPI: $\chi^2 = 2.6$; $p = 0.61$), and its less active (−)-enantiomer, SCH23388 (ASR: $\chi^2 = 1.6$; $df = 3$; $p = 0.66$; $n = 11$; PPI: $\chi^2 = 3.7$; $p = 0.29$) did not significantly affect either ASR or PPI.

The DA D_2 antagonists, haloperidol (ASR: $\chi^2 = 5.3$; $df = 4$; $p = 0.26$; $n = 12$; PPI: $\chi^2 = 13.1$; $p = 0.010$), raclopride (ASR: $\chi^2 = 4.5$; $df = 4$; $p = 0.34$; $n = 12$; PPI: $\chi^2 = 11.4$; $p = 0.022$), and (−)FLA-797 (ASR: $\chi^2 = 5.8$; $df = 3$; $p = 0.12$; $n = 15$; PPI: $\chi^2 = 10.0$; $p = 0.017$), increased PPI without significantly altering ASR. Two other DA D_2 antagonists, the very potent salicylamide, NCQ-298 (ASR: $\chi^2 = 2.0$; $df = 3$; $p = 0.57$; $n = 12$; PPI: $\chi^2 = 0.53$; $p = 0.91$), and the less potent benzamide, remoxipride (ASR: $\chi^2 = 3.1$; $df = 4$; $p = 0.55$; $n = 12$; PPI: $\chi^2 = 3.2$; $p = 0.52$), did not affect ASR or PPI.

Clozapine, which has affinity for a variety of receptors, caused a marked decrease in ASR at the highest dose used (ASR: $\chi^2 = 22.3$; $df = 3$; $p < 0.0001$; $n = 12$). No significant change in PPI was noted (PPI: $\chi^2 = 1.9$; $p = 0.59$). The serotonin-5-HT_2 and DA D_2 antagonist risperidone caused a decrease in ASR at all doses tested ($\chi^2 = 25.8$; $df = 3$; $p < 0.001$; $n = 12$) and a decrease in PPI at the two highest doses ($\chi^2 = 13.7$; $p = 0.003$).

Serotonin Receptor Active Drugs

The 5-HT_{1A} agonist, (+)8-OH-DPAT, elevated ASR ($\chi^2 = 13.7$; $df = 3$; $p = 0.0034$; $n = 11$) at the two highest doses tested and, at the highest dose, diminished PPI ($\chi^2 = 9.6$; $p = 0.022$). Buspirone, a 5-HT_{1A} agonist that is also a DA D_2 antagonist, elevated ASR ($\chi^2 = 11.1$; $df = 3$; $p = 0.011$; $n = 16$) at the highest dose tested and increased PPI ($\chi^2 = 9.7$; $p = 0.022$) at the two highest doses. (−)UH-301, a 5-HT_{1A} antagonist, caused a diminished ASR ($\chi^2 = 15.1$; $df = 3$; $p = 0.0017$; $n = 12$) at the highest dose tested, whereas PPI ($\chi^2 = 7.8$; $p = 0.05$) was slightly diminished at the two higher doses. The 5-HT_2 agonist, DOB, decreased both ASR ($\chi^2 = 22.9$; $df = 3$; $p < 0.0001$; $n = 12$) and PPI ($\chi^2 = 21.7$; $p < 0.0001$) but only at a very high dose, whereas the 5-HT_2 antagonist, ritanserin, affected none of the measures (ASR: $\chi^2 = 4.4$; $df = 3$; $p = 0.22$; $n = 12$; PPI: $\chi^2 = 2.8$; $p = 0.43$).

DISCUSSION

It has been reported that antipsychotic and putative antipsychotic drugs may increase or facilitate PPI in rats (12,27, 36). However, no systematic investigation has been performed to evaluate this contention. In line with this suggestion, Adler et al. (1), using the closely related but not identical measure, the auditory P50 evoked potential paradigm [for comparison between the two measures, see (28)], reported an increased inhibition of the P50 potential after treatment with haloperidol. In the present study, PPI was facilitated by treatment with the DA D_2 antagonists, haloperidol, raclopride and (−)FLA-797 (a metabolite of remoxipride) (22), but not with the DA D_1 antagonists, SCH23390, or its less active isomer, SCH23388. Buspirone, which has D_2 antagonist properties (37), also increased PPI. DA D_2 antagonism seems not to be a sufficient prerequisite for this effect, however, because the very potent and selective DA D_2 antagonist, NCQ-298 (10), and the selective DA D_2 antagonist, remoxipride (39), were inactive on this measure.

In agreement with earlier studies (18,19), diminished PPI was seen after treatment with the NMDA antagonists PCP, MK-801, and ketamine. The DA D_2 agonists quinpirole and (+)3-PPP, as well as the D_1/D_2 agonist apomorphine and the indirectly acting DA agonist, *d*-amphetamine (7,20,24,32,34; and the present study) also decrease PPI. (−)UH-301 at higher doses displayed a similar trend. This may be explained by the rather potent DA D_2 agonistic property of (−)UH-301 (11).

A drug-induced decrease in PPI concomitant with a pronounced decrease in ASR can potentially be explained by sedation. This is probably the case after the administration of high doses of risperidone and clozapine, both of which are strongly sedative. Thus, these substances reduced spontaneous locomotor activity in rats with an ED_{50} of 0.63 and 1.8 μmol/kg, respectively. [The ED_{50} is defined as the SC dose required to reduce activity in rats to 50% of the control level; see (13)].

In the groups treated with PCP and (+)MK-801, higher doses caused a decreased ASR concomitant with a diminished PPI, whereas, at an intermediate dose interval, ASR was elevated and PPI diminished. The 5-HT_{1A} agonist, (+)8-OH-DPAT, induced a dose-related increase in ASR and at higher doses a decrease in PPI. Thus, at least in animals free from ataxia or sedation, there seems to be little correlation between ASR and PPI.

5-HT_2 receptor antagonism, which is a prominent component of risperidone (14,17) and clozapine (21), was probably not involved in the results obtained in the present study, as

TABLE 1

ACOUSTIC STARTLE RESPONSE

Drug Dose (μmol/kg SC)	Startle Amplitude* [Mean ± SEM (Arbitrary Units)]	Prepulse Inhibition of Startle Amplitude* [Mean ± SEM (Percentage)]
PCP		
0	549 ± 47	63 ± 5
0.72	642 ± 46†	55 ± 5
3.6	698 ± 67†	34 ± 5§
7.2	460 ± 59	11 ± 7§
(+)MK-801		
0	859 ± 75	59 ± 5
0.15	1213 ± 145‡	21 ± 6‡
0.3	1107 ± 92†	7 ± 6‡
1.5	563 ± 137†	16 ± 10†
(−)MK-801		
0	905 ± 152	48 ± 5
0.15	919 ± 109	39 ± 4†
0.3	951 ± 111	39 ± 5
1.5	978 ± 95	15 ± 5‡
Ketamine		
0	275 ± 48	75 ± 4
9	367 ± 66†	76 ± 5
18	338 ± 67	57 ± 8†
36	288 ± 83	15 ± 14‡
Apomorphine		
0	101 ± 23	71 ± 5
2.5	260 ± 30‡	37 ± 7‡
4.9	281 ± 31‡	37 ± 8‡
9.9	301 ± 36‡	39 ± 8‡
d-*Amphetamine*¶		
0	224 ± 30	80 ± 4
2.7	277 ± 41	52 ± 5§
5.4	290 ± 36	49 ± 4§
11	280 ± 44	36 ± 5§
(−)-3-PPP		
0	261 ± 35	86 ± 2
2	228 ± 35	78 ± 5
10	224 ± 32	80 ± 4
49	226 ± 41	76 ± 5
(+)-3-PPP		
0	240 ± 30	85 ± 3
2	210 ± 44	74 ± 5†
10	136 ± 22†	69 ± 5‡
49	113 ± 15‡	61 ± 6‡
(+)-SCH-23390		
0	256 ± 34	83 ± 3
0.025	222 ± 26	81 ± 4
0.1	270 ± 58	81 ± 5
0.4	201 ± 33	80 ± 6
1.6	215 ± 29	85 ± 4
(−)-SCH-23388		
0	287 ± 51	84 ± 2
0.1	290 ± 60	70 ± 8
0.4	285 ± 67	78 ± 5
1.6	280 ± 47	81 ± 3
Haloperidol		
0	697 ± 56	57 ± 5
0.075	634 ± 57	60 ± 5
0.3	595 ± 88	71 ± 4‡
0.75	615 ± 97	72 ± 5‡
3.0	504 ± 94	71 ± 3†
Raclopride		
0	564 ± 60	42 ± 5
0.3	535 ± 49	48 ± 8
1.25	485 ± 46	51 ± 6
5	498 ± 45	54 ± 5†
20	432 ± 50	59 ± 7‡
(−)-FLA-797		
0	331 ± 47	72 ± 6
0.1	328 ± 42	80 ± 3
0.4	428 ± 74	79 ± 5
0.8	434 ± 77	86 ± 4†
NCQ-298		
0	209 ± 30	78 ± 4
0.025	217 ± 38	77 ± 4
0.4	221 ± 50	76 ± 7
1.6	269 ± 85	73 ± 8
Remoxipride		
0	577 ± 52	49 ± 5
8	566 ± 79	48 ± 6
16	481 ± 47	47 ± 8
32	535 ± 61	46 ± 7
64	566 ± 74	56 ± 6
Risperidone		
0	148 ± 28	73 ± 4
0.25	97 ± 21†	62 ± 7
1.0	103 ± 37†	60 ± 6†
4.0	41 ± 8‡	38 ± 7‡
Clozapine		
0	663 ± 99	49 ± 7
0.5	620 ± 66	57 ± 7
2	623 ± 97	67 ± 5
8	183 ± 58‡	42 ± 16
(+)8-OH-DPAT		
0	254 ± 57	84 ± 2
0.48	294 ± 57	82 ± 3
1.5	452 ± 72‡	79 ± 3
4.4	535 ± 79‡	70 ± 4†
(−)UH-301		
0	340 ± 51	90 ± 2
2.5	372 ± 84	85 ± 3
10	264 ± 52	74 ± 5‡
40	142 ± 26‡	74 ± 7†
Buspirone		
0	276 ± 62	73 ± 5
3	244 ± 55	73 ± 7
10	268 ± 54	85 ± 2†
30	413 ± 73†	88 ± 2‡
DOB		
0	364 ± 89	86 ± 3
0.03	379 ± 66	88 ± 2
0.3	317 ± 86	82 ± 4
3	86 ± 24	46 ± 9‡
Ritanserin		
0	221 ± 39	77 ± 4
0.2	184 ± 34	75 ± 5
0.8	196 ± 32	81 ± 2
3.2	205 ± 28	74 ± 4

*Startle amplitude (P) is the response when only the main pulse is given as acoustic stimulus. Prepulse Inhibition (PP) of Startle Amplitude is the response when the combination prepulse + main pulse is given as stimulus. Prepulse Inhibition is presented as 100 − ((PP/P)x100), after calculating that quotient for every individual animal. Statistics: † = $p \leq 0.05$; ‡ = $p \leq 0.01$; § = $p \leq 0.001$ vs. the corresponding vehicle treatment condition (Wilcoxon T-test in the case of a significant Friedman test.). ¶1 μmol *d*-amphetaminesulfate = 2 μmol *d*-amphetamine.

ritanserin, a 5-HT_2 antagonist (26), and SCH23390, which also possesses this property (3), were inactive. However, it cannot be excluded that the 5-HT_2 receptor antagonism of drugs such as risperidone and clozapine can indirectly influence DA neuronal function (30).

If diminished PPI reflects a dissociative state in the individual, then the 5-HT_{1A} receptor agonist effect, as displayed by (+)8-OH-DPAT and other 5-HT_{1A} agonists on PPI (25), might be an unwanted property of these drugs. In the present study, the dose of (+)8-OH-DPAT required to cause a significant decrease in PPI is in the dose range commonly regarded to involve postsynaptic 5-HT_{1A} receptors.

One widely used estimate of a drug's antipsychotic potential is its ability to block amphetamine- or PCP-induced hyperlocomotion. In a previous paper we compared the ability of various antipsychotics to block amphetamine- and PCP-induced hyperlocomotion and to inhibit spontaneous locomotion in the rat (13). By comparing these earlier data with the present results, it can be observed that haloperidol, which most potently blocked the different measures of locomotion, is equally potent in increasing PPI. Raclopride is more potent in affecting locomotion than in increasing PPI and FLA-797 (unpublished data) is also slightly more potent in the locomotor measures. Remoxipride and clozapine, which did not affect PPI in the present study, were able to antagonise the effect of amphetamine and phencyclidine on locomotor activity. Thus, in general, the ability of these drugs to influence the locomotor measures seemed more predictive of antipsychotic action than their ability to enhance PPI.

There are some indications that the antipsychotic properties of a drug may be related to its ability to reverse the disruption of PPI induced by DA agonists or noncompetitive NMDA antagonists (2,15,33,38). The functional significance of the facilitatory effect on PPI by some of antipsychotics is less clear, however. Further studies are needed to explore this effect.

The present data show that various antipsychotics and related agents interfere with sensorimotor mechanisms in the rat in different ways. A major finding is that drug-induced changes in PPI occur independently of changes in ASR. Furthermore, the enhancement in PPI induced by some antipsychotics is not related to the antipsychotic activity of these drugs.

ACKNOWLEDGEMENTS

J. Z. and L. S. were supported by grants from the Swedish Medical Research Council (4247).

REFERENCES

1. Adler, L. E.; Rose, G.; Freedman, R. Neurophysiological studies of sensory gating in rats: Effects of amphetamine, phencyclidine and haloperidol. Biol. Psychiatry 21:787–798; 1986.
2. Bakshi, V.; Swerdlow, N. R.; Geyer, M. A. Clozapine antagonizes phencyclidine-induced deficits in sensorimotor gating of the startle response. J. Pharmacol. Exp. Ther. 271:787–794; 1994.
3. Bischoff, S.; Heinrich, M.; Sonntag, J. M.; Krauss, J. The D_1 dopamine receptor antagonist SCH 23390 also interacts potently with brain serotonin (5-HT_2) receptors. Eur. J. Pharmacol. 129: 367–370; 1986.
4. Braff, D. L.; Geyer, M. A. Sensorimotor gating and schizophrenia. Arch. Gen. Psychiatry 47:181–188; 1990.
5. Braff, D. L.; Grillon, C; Geyer, M. A. Gating and habituation of the startle reflex in schizophrenic patients. Arch. Gen. Psychiatry 49:206–215; 1992.
6. Cadenhead, K. S.; Geyer, M. A.; Braff, D. L. Impaired startle prepulse inhibition and habituation in patients with schizotypal personality disorder. Am. J. Psychiatry 150:1862–1867; 1993.
7. Davis, M.; Mansbach, R. S.; Swerdlow, N. R.; Campeau, S; Braff, D. L.; Geyer, M. A. Apomorphine disrupts the inhibition of acoustic startle induced by weak prepulses in rats. Psychopharmacology 102:1–4; 1990.
8. Geyer, M. A.; Swerdlow, N. R.; Mansbach, R. S.; Braff, D. L. Startle response models of sensorimotor gating and habituation deficits in schizophrenia. Brain Res. Bull. 25:485–498; 1990.
9. Grillon, C.; Ameli, R.; Charney, D. S.; Krystal, J.; Braff, D. Startle gating deficits occur across prepulse intensities in schizophrenic patients. Biol. Psychiatry 32:939–943; 1992.
10. Hall, H.; Högberg, T.; Halldin, C.; Köhler, C.; Ström, P.; Ross, S. B.; Larsson, S. A.; Farde, L. NCQ-298, a new selective iodinated salicylamide ligand for the labelling of dopamine D_2 receptors. Psychopharmacology 103:6–18; 1991.
11. Hillver, S. E.; Björk, L.; Yi-Lin, L.; Svensson, B.; Ross, S.; Anden, N.-E.; Hacksell, U. (S)-5-Fluoro-8-hydroxy-2-(dipropylamin)tetralin: A putative 5-HT_{1A}-receptor antagonist. J. Med. Chem. 33:1541–1544; 1990.
12. Hoffman, D. C.; Donovan H. D_1 and D_2 dopamine receptor antagonists reverse prepulse inhibition deficits in an animal model of schizophrenia. Psychopharmacology 115:447–453; 1994.
13. Jackson, D. M.; Johansson, C.; Lindgren L.-M.; Bentsson, A. Dopamine receptor antagonists block amphetamine and phencyclidine-induced motor stimulation in rats. Pharmacol. Biochem. Behav. 48:465–471; 1994.
14. Janssen, P. A. J.; Niemegeers, C. J. E.; Awouters, F.; Schellekens, K. H. L.; Megens, A. A. H. P.; Meert, T. F. Pharmacology of risperidone (R 64 766), a new antipsychotic with serotonin-S_2 and dopamine-D_2 antagonistic properties. J. Pharmacol. Exp. Ther. 244:685–693; 1988.
15. Johansson, C.; Jackson, D. M.; Svensson, L. The atypical antipsychotic, remoxipride, blocks phencyclidine-induced disruption of prepulse inhibition in the rat. Psychopharmacology 116:437–442; 1994.
16. Keith, V. A.; Mansbach, R. S.; Geyer, M. A. Failure of haloperidol to block the effects of phencyclidine and dizocilpine on prepulse inhibition of startle. Biol. Psychiatry 30:557–566; 1991.
17. Leysen, J. E.; Gommeren, W.; Eens, A.; de Chaffoy de Courcelles, D.; Stoof, J. C.; Janssen, P. A. J. Biochemical profile of risperidone, a new antipsychotic. J. Pharmacol. Exp. Ther. 247: 661–670; 1988.
18. Mansbach, R. S.; Geyer, M. A. Parametric determinants in prestimulus modification of acoustic startle: Interaction with ketamine. Psychopharmacology 105:162–168; 1991.
19. Mansbach, R. S.; Geyer, M. A. Effects of phencyclidine and phencyclidine biologs on sensorimotor gating in the rat. Neuropsychopharmacology 2:299–308; 1989.
20. Mansbach, R. S.; Geyer, M. A.; Braff, D. L. Dopaminergic stimulation disrupts sensorimotor gating in the rat. Psychopharmacology 94:507–514; 1988.
21. Meltzer, H. Y.; Gudelsky, G. A. Dopaminergic and serotonergic effects of clozapine. Implications for a unique clinical profile. Arzneimittelforschung 42:268–272; 1992.
22. Mohell, N.; Sällemark, M.; Rosqvist, S.; Malmberg, Å.; Högberg, T.; Jackson, D. M. Binding characteristics of remoxipride and its metabolites to dopamine D_2 and D_3 receptors. Eur. J. Pharmacol. 238:121–125; 1993.
23. Ornitz, E. M.; Hanna, G. L.; de Traversay, J. Prestimulation-induced startle modulation in attention-deficit hyperactivity disorder and nocturnal enuresis. Psychophysiology 29:437–451; 1992.
24. Peng, R. Y.; Mansbach, R. S.; Braff, D. L.; Geyer, M. A. A D_2 dopamine receptor agonist disrupts sensorimotor gating in rats. Implications for dopaminergic abnormalities in schizophrenia. Neuropsychopharmacology 3:211–218; 1990.
25. Rigdon, G. C.; Weatherspoon, J. K. 5-Hydroxytryptamine 1a receptor agonists block prepulse inhibition of acoustic startle reflex. J. Pharmacol. Exp. Ther. 263:486–493; 1992.
26. Schotte, A.; de Bruyckere, K.; Janssen, P. F. M.; Leysen, J. E.

Receptor occupancy by ritanserin and risperidone measured using ex vivo autoradiography. Brain Res. 500:295-301; 1989.
27. Schwarzkopf, S. B.; Bruno, J. P.; Mitra, T. Effects of haloperidol and SCH 23390 on acoustic startle and prepulse inhibition under basal and stimulated conditions. Prog. Neuropsychopharmacol. Biol Psychiatry 17:1023-1036; 1993.
28. Schwarzkopf, S. B.; Lamberti, J. S.; Smith, D. A. Concurrent assessment of acoustic startle and auditory P50 evoked potential measures of sensory inhibition. Biol. Psychiatry 33:815-828; 1993.
29. Simons, R. F.; Giardina, B. D. Reflex modification in psychosis-prone young adults. Psychophysiology 29:8-16; 1992.
30. Svensson, T. H.; Mathé, J. M.; Andersson, J. L.; Nomikos, G. G.; Hildebrand, B. E.; Marcus, M. Mode of action of atypial neuroleptics in relation to the phencyclidine model of schizophrenia: Role of 5-HT_2- and a_1-receptor antagonism. J. Clin. Psychopharmacology; in press.
31. Swerdlow, N. R.; Benbow, C. H.; Zisook, S.; Geyer, M. A.; Braff, D. L. A preliminary assessment of sensorimotor gating in patients with obsessive compulsive disorder. Biol. Psychiatry 33: 298-301; 1993.
32. Swerdlow, N. R.; Braff, D. L.; Masten, V. L.; Geyer, M. A. Schizophrenia-like sensorimotor gating abnormalities in rats following dopamine infusion into the nucleus accumbens. Psychopharmacology 101:414-420; 1990.
33. 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.
34. 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 108:189-195; 1992.
35. Swerdlow, N. R.; Caine, S. B.; Geyer, M. A.; Swenson, M. R.; Downs, N. S.; Braff, D. L. Sensorimotor gating deficits in schizoprenia and Huntington's disease and in rats after manipulation of hippocampus-accumbens circuitry. Presented at the International Congress on Schizoprenia Research, Tucson, Arizona, 1991.
36. Swerdlow, N. R.; Geyer, M. A. Clozapine and haloperidol in an animal model of sensorimotor gating deficits in schizophrenia. Pharmacol. Biochem. Behav. 44:741-4; 1993.
37. Tunnicliff, G. Molecular basis of buspirone's anxiolytic action. Pharmacol. Toxicol. 69:149-56; 1990.
38. Wiley, J. L. Clozapine's effects on phencyclidine-induced disruption of prepulse inhibition of the acoustic startle response. Pharmacol. Biochem. Behav. 49:1025-1028; 1994.
39. Ögren, S. O.; Hall, H.; Köhler, C.; Magnusson, O.; Lindbom, L.-O.; Ängeby, K.; Florvall, L. Remoxipride, a new potential antipsychotic compound with selective antidopaminergic actions in the rat brain. Eur. J. Pharmacol. 102:459-474; 1984.