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Dopamine Receptor Antagonists Block Amphetamine and Phencyclidine-Induced Motor Stimulation in Rats

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JACKSON, D. M., C. JOHANSSON., L.-M. LINDGREN AND A. BENGTSSON. *Dopamine receptor antagonists block amphetamine and phencyclidine-induced motor stimulation in rats.* PHARMACOL BIOCHEM BEHAV **48**(2) 465–471, 1994.—*d*-Amphetamine (DEX) and phencyclidine (PCP) increased motor activity in rats as measured in automated activity cages. Analysis of the stimulation indicated that both drugs increased horizontal activity (total activity), locomotion, and peripheral activity. However, DEX increased while PCP decreased the incidence of rearing. The ability of different drugs to antagonise DEX- and PCP-induced increases in total activity (called stimulation) was measured. Dopamine (DA) D_1 receptor antagonists (SCH23390, NNC-01-0112) were 7–8 times more potent in blocking DEX than PCP. DA D_2 receptor antagonists (raclopride, remoxipride, haloperidol) were only 1–2 times more potent against DEX-induced stimulation. Nonselective DA receptor antagonists were also tested. Chlorpromazine was more potent against DEX than against PCP. Buspirone and sertindole were slightly more potent in blocking PCP than DEX. Ritanserin (5-HT_2 receptor antagonist) was inactive against both stimulants. 8-OH-DPAT (5-HT_{1A} receptor agonist) potentiated the stimulant effects of DEX and PCP. Prazosin (α_1-adrenergic receptor antagonist) partially blocked both DEX and PCP. Most drugs tested depressed spontaneous motor activity. Remoxipride and sertindole, however, caused very little depression even at doses several times higher than those needed to block DEX or PCP. The data show clear pharmacological differences between DEX- and PCP-induced stimulation.

Dopamine receptors Dopamine D_1 receptor Dopamine D_2 receptor Phencyclidine *d*-Amphetamine Motor activity

ONE of the most important supports for the dopamine (DA) hypothesis of schizophrenia comes from the observation that *d*-amphetamine (DEX) can mimic some of the florid or positive symptoms of schizophrenia, including hallucinations and paranoid thoughts [see (16) for discussion and further original references]. There is no clear sign of negative symptoms such as anergia and autism after DEX usage. However, substances other than DEX can also induce psychiatric disorders. One of these is phencyclidine (PCP, 1-[1-phenylcyclohexyl]piperidine) which, unlike DEX, produces a syndrome that includes components that resemble negative symptoms of schizophrenia (9,10,22). Attempts have been made to translate these chance clinical observations into preclinical research in an attempt to develop new animal models of psychosis.

Preclinically, there are both similarities and differences between DEX and PCP. For example, both drugs can stimulate motor activity in rodents. DEX exerts its stimulant effects via the release of newly synthesized DA (27,31), primarily in the nucleus accumbens (20), and has no direct effect on glutamate receptors. DEX in high doses can also release noradrenaline and this can contribute to the behavioural stimulation (34). While PCP also stimulates rodent motor activity (15,23,33), it interacts with at least three separate sites in the central nervous system. Firstly, it binds noncompetitively as an antagonist (4) to a site inside the NMDA ion channel and blocks NMDA currents in a voltage-dependent way. Secondly, it can both release DA and inhibit its uptake in slice preparations and synaptosomes (35). Thirdly, it has a relatively low affinity for haloperidol-sensitive sigma binding sites [(28,29), and see (25) for review].

Because of these two common properties shared by DEX and PCP, i.e., ability to produce some psychotic symptoms in humans and ability to induce motor activity in rodents, we addressed two main questions in the present paper. First, are

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the stimulations induced by DEX and PCP quantitatively and qualitatively similar? Second, are the stimulations sensitive in a similar way to various pharmacological manipulations? To answer the second question, we examined the sensitivity of these stimulations to blockade by various antipsychotics, putative antipsychotics, selective DA D_1 receptor antagonists and some control substances.

METHOD

Animals

Male Sprague-Dawley rats (B & K Universal AB, Sollentuna, Sweden) weighing between 250 and 350 g were used. They were maintained on a diurnal cycle of 12 D : 12 L (lights on at 0600 h in the morning) and were kept in the laboratory environment for 5 to 7 days before use. Food pellets and tap water was available ad lib, except for the period in the activity cages. The experiments were run during the light phase. Each animal was used only once.

Apparatus

Seven Plexiglas activity cages from Kungsbacka mät-och reglerteknik AB, Fjärås, Sweden, with a floor area of 700 × 700 mm, were used. They were housed in soundproofed ventilated boxes with no lighting. These activity boxes have been described in detail elsewhere (11). Briefly, two rows of photocells (total 16 photocells, one row at floor level, the other row placed higher to measure rearing) enable a computer-based system to determine the location of the animal at any time. In the present study, we measured variables that we have designated as follows. Horizontal activity represents the total number of times lightbeams in the lower row were interrupted—this measure is used in the present study as a measure of total activity; peripheral activity represents the breaking of beams that are located closest to one of the four walls; locomotion represents crossing of a sequence of beams one after the other and, thus, represents movement in a single direction; corner time represents the time an animal spends in any one of the four corners NOT moving; rearing represents the interruption of the upper row of lightbeams.

Drugs

Remoxipride hydrochloride monohydrate and raclopride tartrate were synthesized in the chemical laboratories of Astra Arcus AB. Other drugs were obtained as follows: (+) NNC-01-0112 (gift of Novo Nordisk, Denmark), prazosin hydrochloride, PCP hydrochloride, 8-OH-DPAT (8-hydroxy-*N,N*-di-n-propyl-2-aminotetraline) and SCH23390 (7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride) (Research Biochemicals Inc., Natick, MA), haloperidol, buspirone and chlorpromazine (Sigma Chemical Company, St. Louis, MO), ritanserin and risperidone (gifts of Janssen Pharmaceutica, Belgium), sertindole (gift of Dr. J. Arnt, Lundbeck A/S, Denmark), clozapine (gift of Sandoz, Switzerland), DEX sulphate (Calaise Chimie S.A., France).

DEX, PCP, raclopride, and remoxipride were dissolved in saline. Clozapine, haloperidol, NNC-01-0112, prazosin, risperidone, ritanserin, and sertindole were dissolved in a minimum of glacial acetic acid and diluted in distilled water. SCH23390 was dissolved in a few drops of propanediol and diluted to volume with distilled water. Buspirone was dissolved in distilled water, and chlorpromazine and 8-OH-DPAT in normal saline. The pH of the final injected solutions was between 4.2 and 5.7. All drugs were injected subcutaneously in the neck, in a volume of 2 ml/kg.

Experimental Procedure

Dose–response curves were generated for both DEX and PCP as follows. Rats were placed into the activity cages for 30 min. They were then injected with saline, DEX, or PCP and placed back into the cages for a period of 1 h, during which time motor activity was measured each 1 min.

When assessing the potency of various substances to depress spontaneous activity and to block DEX or PCP, test antagonist drugs were injected 60 min prior to DEX or PCP. The animals were put back into their home cages for 30 min and then transferred into the activity boxes for a period of 30 min. During this period, activity was registered and the data used to estimate the depressant effect of each test substance (i.e., in the absence of any agonist). The rats were then injected with DEX (5 μmol/kg, equivalent to 0.9 mg/kg) or PCP (14.3 μmol/kg, equivalent to 4 mg/kg), put back into their previous activity boxes, and activity was measured for 1 h.

Statistics

In the first experiment (Fig. 1), where the effects of PCP and DEX alone were studied, the data are expressed as the mean number of events ± SEM during the hour immediately following agonist administration. Data were analyzed using a single-factor ANOVA, and in the case of a significant effect, Dunnett's multiple range test as the post hoc analysis.

Where the effect of the various antagonists (in the absence of DEX and PCP challenge) was studied, the raw data, expressed as the total number of events during the 30-min period (i.e., after the various test drugs but before DEX or PCP challenge) was used to calculate an ED_{50} value which represents the calculated dose of antagonist required to reduce the activity in rats challenged with the test drug vehicle by 50%, i.e., to half.

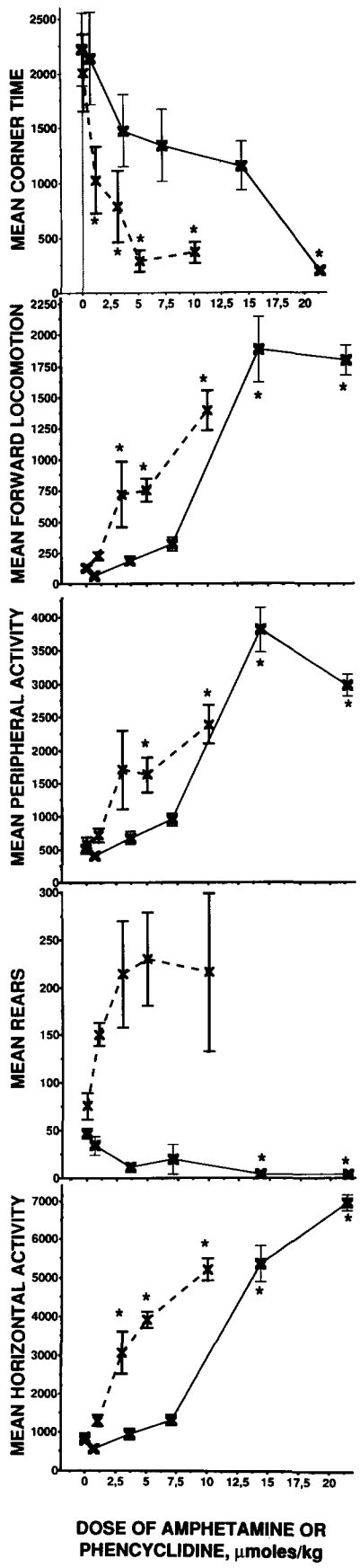
An ED_{50} value has also been calculated to described the ability of the various test substances to block DEX and PCP. This is the calculated dose required to reduced by 50% the total activity of animals pretreated with test drug vehicle and challenged with DEX or PCP.

All ED_{50} values were calculated using linear regression, and the 95% confidence interval was calculated according to Fieller's theorem.

At least three doses of the test drug were studied, with 5–11 animals in each treatment group. At least one dose of the test substance was greater and one dose of the test substance was lower than the subsequently calculated ED_{50} value.

RESULTS

Both DEX and PCP produced dose-dependent increases in horizontal activity (total activity), peripheral activity, and locomotion (Fig. 1). This increased activity was mirrored by a dose-dependent decrease in corner time after each stimulant. A clear difference in the response to both drugs was seen in the rearing response—DEX dose dependently but nonsignificantly increased the incidence of rearing while PCP decreased the incidence of this behavior. The nonsignificant result with DEX was due to the high variance seen after the highest dose (10 μmol/kg) (see the Discussion section). When the data were reanalyzed without the highest dose data, the increase in rearing became significant, $F(3, 30) = 3.84$, $p < 0.021$), with



post hoc tests indicating that both 3 and 5 μmol/kg doses caused a significant increase in rearing. From these dose-response curves, 5 μmol/kg DEX and 14.3 μmol/kg PCP were chosen for the antagonism experiments. In the following experiments, except where otherwise mentioned, the data described represent the horizontal activity parameter (called stimulation). These data are summarized in Table 1.

The DA D_1 receptor antagonists SCH23390 and NNC-01-0112 blocked the stimulation produced by both DEX and PCP. However, both were much more potent in blocking the stimulation induced by DEX than that by PCP. The selective DA D_2 receptor antagonists, raclopride and remoxipride, as well as haloperidol, were also effective antagonists of both stimulants, but showed no large difference in their ability to block DEX compared to PCP. Of the other compounds tested, chlorpromazine was more potent in blocking DEX than PCP, so in this regard resembled the DA D_1 receptor antagonists. Clozapine was slightly more potent in blocking DEX than PCP-induced activity, while risperidone was equipotent against both stimulants. Ritanserin was inactive. In contrast to all other active substances tested, both buspirone and sertindole were slightly more effective in blocking PCP than DEX-induced activities.

Several of the antagonists tested (chlorpromazine, clozapine, risperidone, sertindole) exhibit substantial affinity for α_1-adrenergic receptors. The selective α_1-adrenergic receptor antagonist, prazosin, at a dose of 2.4 μmol/kg (1 mg/kg) blocked PCP-induced stimulation by about 36%, while a dose of 0.95 μmol/kg (0.4 mg/kg) blocked DEX-induced stimulation by about 42%. Because buspirone has a considerable affinity for 5-HT_{1A} receptors (about 10 nM), rats were premedicated with either vehicle or 8-OH-DPAT (0.31 or 3.05 μmol/kg, 0.1 or 1.0 mg/kg, respectively) and then challenged with DEX or PCP. The high dose of 8-OH-DPAT significantly potentiated both DEX- and PCP-induced stimulation (Table 1, footnote).

The activity data was further analyzed in the case of NNC-01-0112 (a representative DA D_1 receptor antagonist) and raclopride (a representative DA D_2 receptor antagonist) and the effect of these substances on the individual behaviors (horizontal activity, peripheral activity, locomotion, and corner time) affected by DEX and PCP examined (data not shown). Both NNC-01-0112 and raclopride dose dependently blocked the increased horizontal activity, locomotion, and peripheral activity induced by both agonists. In the case of rearing, both antagonists dose dependently blocked the increased rearing

FIG. 1. The effect of various doses of DEX (X----X) and PCP (X——X) on various aspects of motor activity in rats. The activity was broken down to various components, mean corner time, mean locomotion, mean peripheral activity, mean rears, and mean horizontal activity. The data represent the mean activity in 1 h ± SEM. After a significant single factor analysis of variance was obtained, the data were further analyzed with post hoc Dunnett's multiple comparison tests. Statistical results are as follows: mean corner time: effect of PCP, $F(5, 49) = 7.29$, $p < 0.001$; effect of DEX, $F(4, 39) = 8.01$, $p < 0.001$; mean locomotion: effect of PCP, $F(5, 49) = 55.82$, $p < 0.001$; effect of DEX, $F(4, 39) = 14.45$, $p < 0.001$; mean peripheral activity: effect of PCP, $F(5, 49) = 77.84$, $p < 0.001$; effect of DEX, $F(4, 39) = 6.48$, $p = 0.001$; Mean rears: effect of PCP, $F(5, 49) = 3.15$, $p = 0.016$; effect of DEX (all data), $F(4, 39) = 1.58$, $p = 0.2$; mean horizontal activity: effect of PCP, $F(5, 49) = 171.96$, $p < 0.001$; effect of DEX, $F(4, 39) = 43.79$, $p < 0.001$. Significant post hoc tests are indicated on the graph ($p < 0.05$, *compared to the appropriate saline control).

TABLE 1

THE ABILITY OF VARIOUS DRUGS TO ANTAGONISE DEX- AND PCP-INDUCED STIMULATION AND TO DEPRESS SPONTANEOUS ACTIVITY DURING THE PERIOD PRIOR TO INJECTION OF DEX OR PCP

Test Substance	Amphetamine		Phencyclidine		Ratio*	Activity During Preagonist Period ED_{50}† (Confidence Limits)	
	ED_{50}	Confidence Limits	ED_{50}	Confidence Limits			
Selective D_1 antagonists							
SCH23390	0.05	(0.03–0.1)	0.4	(0.2–1.0)	8	0.26	(0.22–0.33)
NNC-01-0112	0.03	(0.01–0.04)	0.2	(0.1–0.4)	6.7	0.05	(0.04–0.07)
Selective D_2 antagonists							
Haloperidol	0.2	(0.1–0.2)	0.4	(0.3–0.5)	2	0.18	(0.15–0.21)
Raclopride	0.8	(0.06–1.1)	1.0	(0.4–2.1)	1.3	0.22	(0.16–0.28)
Remoxipride	6.7	(2.5–12.3)	11.8	(8.7–17.1)	1.8	>60	
Selective $5HT_2$ antagonist							
Ritanserin	>6.7‡		>6.7§			>6.7	
Miscellaneous							
Buspirone	5.7	(1.3–11.1)	3.7	(1.2–6.8)	0.7	1.7	(1.1–2.3)
Chlorpromazine	0.9	(0.6–1.2)	6.8	(5.0–10.6)	7.6	4.4	(3.0–7.1)
Clozapine	2.4	(1.7–3.3)	6.6	(3.9–13.3)	2.8	1.8	(1.4–2.4)
Risperidone	1.1	(0.8–1.6)	1.2	(0.8–2.0)	1.1	0.63	(0.54–0.72)
Sertindole	29.2	(13.9–¶)	13.0	(3.2–34.6)	0.5	>60	
Prazosin	>0.95#		>2.4**			>2.4	
8-OH-DPAT††							

DEX, 5 μmol/kg (0.9 mg/kg) and PCP, 14.3 μmol/kg (4 mg/kg). The data are the ED_{50} values (μmol/kg). The ED_{50} is the dose of test drug required to reduce by 50% (to half) the activity of rats pretreated with saline and given DEX or PCP or, in the case of activity before the agonist, the dose that reduced spontaneous activity to half that of saline animals. At least three doses of each test substance were used to calculate each ED_{50}; one was higher and one was lower than the final calculated ED_{50} value.

*The ratio is the ED_{50} against PCP to that against DEX.

†The ED_{50} value is the dose required to depress activity of control animals (no PCP or DEX) to 50% (95% confidence intervals in parentheses).

‡Doses tested were 0.05, 0.2, 0.8, and 3.2 mg/kg (0.10, 0.42, 1.68, and 6.7 μmol/kg, respectively). All inactive.

§Doses tested were 0.2, 0.8, and 3.2 mg/kg (0.42, 1.68, and 6.7 μmol/kg, respectively.) All inactive.

¶Higher confidence limit could not be calculated.

#Five doses were tested between 0.01 and 0.4 mg/kg (0.02 to 0.95 μmol/kg).

**Three doses were tested between 0.05 and 1.0 mg/kg (0.12 to 2.4 μmol/kg).

††8-OH-DPAT, 0.31 and 3.05 μmol/kg (0.1 and 1.0 mg/kg, respectively) potentiated the DEX response by 8% (not significant) and 84% ($p < 0.001$ by Student's t-test), respectively. The response to PCP challenge was potentiated using the same doses of 8-OH-DPAT by 12% (not significant) and 88% ($p < 0.001$ by Student's t-test), respectively.

caused by DEX but had no effect on the reduction seen after PCP, which was near zero in all cases. No clear pattern was seen in the corner time parameter.

During the 30 min before either DEX, PCP, or vehicle was injected, activity was measured to provide an indication of the various test drugs own effects. Note that the measuring period was immediately before agonist injection. The data are presented as ED_{50} values in Table 1. Spearman rank correlations were calculated (omitting 8-OH-DPAT results), correlating the test drugs' own ED_{50} value and the ED_{50} value against either DEX or PCP. In both cases, a significant positive correlation was noted with p values of 0.008 (DEX) and 0.002 (PCP). In general, drugs that blocked DEX- and PCP-induced activity stimulation also caused depression of spontanous motor activity. Two drugs were, however, exceptional. Thus, remoxipride and sertindole caused no significant depression of spontanous activity, while raclopride was more potent in depressing activity during the habituation phase than in blocking DEX or PCP. Haloperidol was equipotent in all measures.

Because the experiments were run over the course of a year, we wished to ensure that the assay system was reproducible. The experiment with SCH23390 + DEX was repeated. An ED_{50} value (μmol/kg) of 0.044 (0.030–0.062) was obtained, in good agreement with the data in Table 1.

DISCUSSION

Both DEX and PCP increased motor activity, as measured in automated activity cages. This increased activity was evident as increases in horizontal activity, locomotion, and peripheral activity, as well as a decreased time spent in the corners. However, while DEX increased the incidence of rearing, PCP decreased the incidence of this behavior. Although the increase was not significant after DEX if the data from all doses were included in the analysis, it became significant when the 10 μmol/kg data was excluded. The large variation seen with this latter dose is not surprising: the dose was, in terms of rearing, supramaximal (see the figure), and associated with the behavioral response was a large number of diverse and intense stereotypies. Such stereotypies (sniffing at the floor, grooming, etc.) are incompatible with rearing.

The present results are consistent with a previous study in mice reported by Stavchansky et al. (32). These authors noted that while both DEX and PCP increased horizontal activity,

DEX increased vertical activity (rearing) while PCP reduced it. In terms of the involvement of NMDA receptors in rearing behavior, another NMDA receptor antagonist AP-7 (2-amino-7-phosphonoheptanoic acid), after intraventricular injection into rats, produced an increase in distance traveled, speed, and peripheral movement, but no increase in rearing (24). These authors specifically commented on this result in relation to the increased rearing seen after DEX. In addition, dizocilpine (another NMDA receptor antagonist), as well as PCP, was recently reported to reduce rearing (23). It seems then, that NMDA antagonists, in contrast to DEX, reduce the incidence of rearing.

It is clear that DA was a common requirement in the stimulation seen in the present studies after DEX and PCP because all the DA D_1 and D_2 receptor antagonists blocked the stimulation (measured as total activity—see the Method section). However, there were clear differences in the potency of various neuroleptics to block DEX and PCP-induced stimulation, suggesting that pathways other than a purely DA pathway were involved.

Thus, the highly selective DA D_1 receptor antagonists, SCH23390 and NNC-01-0112, were much more potent in blocking DEX than in blocking PCP. [See Andersen et al. (2) for details on this representative of a new series of selective DA D_1 receptor antagonists.] These two agents have similar affinity at DA D_1 receptors (about 0.4 nM, IC_{50} value) with SCH23390 also displaying some 5-HT_2 receptor affinity (2). However, the effect of the SCH23390 was unlikely to be related to its 5-HT_2 receptor blocking capacity for three reasons: first, the selective 5-HT_2 antagonist ritanserin was inactive in the present study; second, risperidone, which has a very high affinity for 5-HT_2 receptors (circa 0.3 nM K_i value) displayed no selectivity in its antagonistic properties, and third, NNC-01-0112 has virtually no 5-HT_2 affinity (2).

In contrast to the DA D_1 receptor antagonists, the DA D_2 receptor antagonists raclopride, remoxipride, and haloperidol displayed little selectivity in their blocking of DEX and PCP. Although haloperidol has some α_1-adrenergic receptor affinity, this is about 30 times less than that for DA D_2 receptors and probably does not play a role in the present studies. Thus, Andén et al. (1) showed that haloperidol produced significant α_1 blocking effects only at doses above about 1 mg/kg (2.66 μmol/kg, much higher than the present ED_{50} values) (and see below for further discussion).

Chlorpromazine, resembling the selective DA D_1 receptor antagonists, was more potent in blocking DEX-induced stimulation. This compound, while being a potent DA D_2 receptor antagonist, also has significant DA D_1 receptor affinity. The D_1 receptor affinity (together with the D_2 receptor affinity) may have contributed to the net blocking effect. On the other hand, Arnt and Hyttel (3) using SKF38393 or pergolide-induced rotation in rats with unilateral lesions of the nigrostriatal DA pathway, showed that chlorpromazine preferentially blocked the pergolide induced rotation—in other words, it behaved in this model as a DA D_2 receptor antagonist. Chlorpromazine has, however, affinity for a variety of receptors other than DA (α_1 histamine H1, muscarinic, 5-HT_2, for example) and these could interact in unpredictable ways to affect different behavioural models.

Only two drugs were more potent in blocking PCP-than DEX-induced stimulation. These were the mainly 5-HT_{1A} agonist compound buspirone and the putative atypical antipsychotic sertindole. Buspirone has relatively weak DA D_2 receptor antagonist properties but potent 5-HT_{1A} receptor agonist properties, while sertindole resembles in some ways clozapine, having a high 5-HT_2 receptor affinity and a somewhat lower DA D_2 receptor affinity (30). Neither has, to our knowledge any affinity at the NMDA receptor. Interestingly, the selective 5-HT_{1A} agonist, 8-OH-DPAT, potentiated both DEX and PCP-induced stimulation, suggesting that the buspirone antagonism was due to its DA D_2 receptor antagonistic actions and not to any 5-HT_{1A}-mediated effects.

The correlation between the ability of the various test compounds to block DEX- and PCP-induced stimulation and their own effect in depressing motor activity was striking and significant in both cases. However, some interesting differences emerged. Thus, remoxipride, even at a dose of 60 μmol/kg, caused no depression of spontanous motor activity even though this dose was about 6 to 10 times higher than the doses required to block PCP and DEX, respectively. In contrast, raclopride was more potent in depressing spontaneous motor activity than in blocking PCP or DEX. Haloperidol was roughly equipotent in all measures. While it cannot be excluded that pharmacokinetic differences could contribute to the present results, the data suggest that there may not be a straight correlation between the ability of a drug by itself to induce depression of spontaneous activity and its ability to block DEX and PCP. The depression of spontaneous motor activity induced by DA receptor antagonists reflects, in large part, the blocking of DA D_1 and/or DA D_2 receptors in the nucleus accumbens and striatum [see (21), Jackson et al. 1989, for detailed discussion].

Some of the test substances (chlorpromazine, clozapine, risperidone, sertindole) have affinity for α_1-adrenergic receptors and block these receptors. Furthermore, it has been well documented that blockade of α_1-adrenergic receptors can diminish (but not completely block) DA receptor agonist-induced stimulation (12). Although high doses of prazosin reduced both DEX and PCP-induced stimulation in the present study, this reduction was less than 50%, in agreement with earlier studies using other stimulants (12). Thus, while α_1-adrenergic antagonism cannot be ruled out as a factor contributing to the blockade obtained with some of the test substances, it is not sufficient to account for all the present results.

What, then, are the mechanisms underlying the differences reported in the present study? Two areas, at least, need to be considered. The first is the neurochemical differences between the two drugs and the second is the way in which DA and glutamate receptors communicate with each other in the central nervous system.

DEX is a catecholamine-related drug that induces the release of DA and, to a lesser extent, noradrenaline, in the CNS and in the periphery (27,31). Both of these transmitters are involved in motor activity (34), with α_1-adrenergic receptor antagonists blocking DA agonist-induced stimulation [this paper and (12)]. DEX has no direct effect on glutamate receptors. In contrast, as mentioned above, PCP is a noncompetitive antagonist at the NMDA type of glutamate receptor (4), it can release DA and inhibit its uptake in slices and synaptosomes (35), and it binds to sigma binding sites (25,28,29). PCPs affinity for the so-called haloperidol-sensitive sigma binding site is low (287 ± 59 nM, IC_{50} value) compared to other ligands (haloperidol, 9.3 ± 0.6 nM; (+)-3-PPP, 31 ± 10) [data from (28)]. It is unknown if the sigma binding site is a neurotransmitter receptor in the classical sense [see (18,19, 28,29,36,37), for various viewpoints], and the question of sigma binding site involvement in PCPs actions will only be clarified when highly selective sigma ligands become available and when a functional assay system that enables agonist and antagonist actions to be determined is available.

It has been known for many years that DA and glutamate receptors have close links in various parts of the central nervous system. Such links occur in two major motor DA systems of the rat brain—the basal ganglia and the mesolimbic-cortical system. In some models, DA function seems to be under excitatory amino acid control with striatal DA release, for example, being stimulated by glutamate via NMDA receptors (7,8,26). There is also a functional interaction within the nucleus accumbens with locally applied NMDA producing marked motor stimulation that resembles that seen after DA agonists (5,17). An interaction is also seen electrophysiologically, with ventral tegmental neurones in the rat being excited by systemic PCP administration (13). It is, however, difficult to use these interactions to explain the current results: if one accepts the strong excitatory amino acid control of at least some DA systems, then one could equally expect that NMDA antagonists would depress motor activity. However, the opposite is the case. In any case, both DEX and PCP (6) release DA within the nucleus accumbens, albeit via different mechanisms, and this DA release almost certainly contributes, at least partly, to the stimulation seen after DEX and PCP. PCP (but not DEX)-induced release of DA in the accumbens was shown to be γ-butyrolactone sensitive, implying a dependence on intact neuron firing in the case of PCP and emphasizing the pharmacological difference between the two substances. French et al. (14) showed that PCP-induced stimulation, although dependent on DA function within the nucleus accumbens, was probably mediated via an interaction with binding sites located on mesolimbic DA terminals within the accumbens.

It might be argued that the potency difference displayed by the neuroleptics in blocking DEX- and PCP-induced excitation could depend on the different stimulation level present after the two behavioural stimulants. Thus, the horizontal activity after DEX challenge (no antagonist present) was in a typical experiment 2946 ± 202 counts in the first hour and after PCP 4429 ± 564. However, it is unlikely that this was an important determinant in the present study. First, the doses of both DEX and PCP were submaximal; second, the DA antagonists tested antagonise both DEX and PCP (via released DA) competitively at DA D_1 or D_2 receptors; third, the blocking pattern exhibited by the DA D_1 receptor antagonists, DA D_2 receptor antagonists and by sertindole, for example, suggests that that effect is influenced mainly by the receptor profile of the drug itself.

It seems clear from the present results that PCP-induced behavioral stimulation depends not only on its direct ability to release DA, but also on its NMDA ion channel interactions and/or its sigma binding properties. As discussed above, there are close anatomical connections between DA and NMDA receptors and these probably provide the explanation for the present results. Thus, DEX- and PCP-induced excitation in rats is qualitatively different. Furthermore, pharmacological differences are also evident, with DA D_1 receptor antagonists being much more potent in blocking DEX- than PCP-induced stimulation, with selective DA D_2 receptor antagonists showing much less selectivity.

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