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Differential effects of classical and newer antipsychotics on the hypermotility induced by two dose levels of D-amphetamine

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Abstract

The inhibitory effects of a variety of established and putative antipsychotic compounds on the hypermotility induced by D-amphetamine at two dose levels (0.5 and 2.0 mg/kg) have been studied. Classical antipsychotics (haloperidol, fluphenazine and cis(*Z*)-flupentixol) and the selective dopamine D_2 receptor antagonist remoxipride inhibit hypermotility in the two conditions with similar potencies, whereas sertindole, clozapine, risperidone, ziprasidone and olanzapine preferentially inhibit the effect of the low dose of D-amphetamine (selectivity ratios between 6.5 and 18). Seroquel, amperozide and the selective 5-HT_{2A} receptor antagonist MDL 100.151 ((±)-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidine-methanol) have no effect on D-amphetamine 2.0 mg/kg, but inhibit the response to D-amphetamine 0.5 mg/kg. The α_1-adrenoceptor antagonist prazosin inhibits the motility response to D-amphetamine 0.5 mg/kg with slightly higher potency than that to D-amphetamine 2.0 mg/kg, whereas the 5-$HT_{2A/2C}$ receptor antagonist ritanserin selectively inhibits the effect of D-amphetamine 0.5 mg/kg. The histamine H_1 receptor antagonist mepyramine is ineffective in both models. All compounds, except remoxipride, MDL 100.151 and ritanserin (which are ineffective) inhibit spontaneous locomotor activity at dose levels close to those inhibiting the response to D-amphetamine 2.0 mg/kg. Prazosin has partial inhibitory effect. In conclusion, dopamine antagonism has similar inhibitory effect on hyperactivity induced by low and high D-amphetamine dosages, α_1-adrenoceptor antagonism also contributes to both effects, whereas 5-HT_2 receptor antagonism selectively interacts with the low D-amphetamine dose. This indicates that the responses to D-amphetamine 0.5 and 2.0 mg/kg are differently modulated by these neurotransmitters. These results indicate that the dose level of D-amphetamine inducing hyperactivity is important for the pharmacology of this response and indicate that different neuronal interactions are involved. The implications of these observations for the improved ratio between efficacy and neurological side-effects of newer antipsychotics are discussed.

Keywords: Dopamine receptor; 5-HT_2 receptor; α_1-Adrenoceptor; Hyperactivity; Amphetamine; (Rat)

1. Introduction

For the last decade the development of new antipsychotic drugs has focussed on drugs having a selective or preferential inhibitory effect on limbic versus nigrostriatal dopamine function. Clozapine is the prototype limbic-selective antipsychotic without the propensity to induce extrapyramidal side effects in comparison with classical antipsychotics, e.g. haloperidol and fluphenazine. Limbic selectivity has been demonstrated using electrophysiological (Chiodo and Bunney, 1985; Skarsfeldt, 1988) and behavioural models (Arnt, 1983; Gardner et al., 1993).

Inhibition of locomotor hyperactivity induced by dopaminergic drugs (e.g. D-amphetamine, apomorphine, etc.) has been a frequently used animal model to the study of limbic dopamine function (Ögren et al., 1984; Arnt et al., 1994; Costall et al., 1980; Sorensen et al., 1993). Lesion and microinjection studies have provided evidence that hypermotility induced by D-amphetamine is mediated preferentially by release of dopamine in the nucleus accumbens (Kelly et al., 1975; Costall et al., 1977,1980).

In addition, other limbic brain regions rich in dopamine have been shown to be involved in regulation of locomotor activity, e.g. tuberculum olfactorium (Costall and Naylor, 1976; Cools et al., 1994). An interaction between frontal cortex and nucleus accumbens dopamine function has been suggested as well (Blanc et al., 1994).

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D-Amphetamine induces dose-dependent hyperactivity, while higher doses induce stereotyped behaviour, which is mediated by increased dopamine function in striatum (Kelly et al., 1975; Costall et al., 1977). Given the above-mentioned heterogeneity of limbic/cortical structures involved in regulation of locomotor activity it may be possible that these structures show differences in sensitivity to D-amphetamine. If so, the pharmacology of these responses may accordingly be different. This hypothesis has been tested in the present study in which a variety of classical and newer antipsychotic drugs have been evaluated for inhibitory potencies against the hypermotility induced by two doses of D-amphetamine, a minimum effective dose, and a dose inducing the maximum hypermotility without focussed stereotyped behaviour, respectively. These experiments provide evidence that the D-amphetamine dose is important for the potencies of antipsychotics and, accordingly, for the receptor specificity of the response. Part of the study has been presented in preliminary form at the XIXth C.I.N.P. Congress, Washington DC, July 1994 (Arnt et al., 1994).

2. Materials and methods

2.1. Animals

Male Wistar rats (Mol:Wist strain, Møllegaard, Denmark) weighing 170-240 g were used. They were housed in groups of four in Macrolon type III cages (high model) in animal rooms at 21 ± 2°C with a relative humidity of 55 ± 10%, air exchange (16 times/h) and day/night cycle (light on 6 a.m.–6 p.m.). They had free access to commercial food pellets (Special Diet Services, type R/MI(E)SQC) and acidified water throughout the study.

2.2. Procedure

Inhibition of D-amphetamine-induced hypermotility

The experiments were made in normal light conditions in an undisturbed room.

In pilot experiments saline or different doses of D-amphetamine (0.25–2.0 mg/kg s.c.) or saline were administered and locomotor activity measured for 2 h.

In the subsequent inhibition studies the test substance or saline was injected s.c. At different time points (see Table legends) D-amphetamine hemisulphate (0.5 or 2.0 mg/kg s.c.) or saline was injected. Immediately after the second injection the rats were placed individually in the test cage (Macrolon type III, high model, using a flat wire mesh lid). The cage was placed in a U-frame, equipped with four infrared light sources and photocells. The light beams cross the cage 4 cm above the bottom of the cage. Recording of a motility count required consecutive interruption of adjacent light beams, thus avoiding high count induced by stationary movements of the rat. The bottom of the cage was covered by a thin layer of standard sawdust bedding material (Finn Tapvei).

Motility was recorded for a period of 2 h. All data were stored in a Paradox database (version 3.5) from which data were exported to the statistical program for further analysis.

Each compound was tested at least twice using overlapping dose levels. The control responses obtained in different experiments were pooled before further statistical analysis given they were not statistically different. Motility counts were analyzed by Kruskal-Wallis analysis of variance, using the Crunch Statistical Program (version 4.0). If the main test showed significant dose effect (P value of 0.05 or lower) comparisons between the control D-amphetamine group and test groups were made post-hoc using a one-sided t-test with adjustment of P level according to Bonferroni. At least seven rats were used in each dose group.

ED_{50} values were calculated by log-probit analysis on basis of the percent inhibition responses obtained at each dose level. They were calculated by subtraction of the baseline motility response (induced by saline + saline) from the drug-induced motility responses and were expressed in percent of the response in the D-amphetamine control groups.

Inhibition of spontaneous locomotor activity

In separate experiments the inhibition of spontaneous exploratory motility was measured in the same way as described above, except that the test is performed in the dark, and that motility was measured for 15 min, beginning 30 min or 2 h (see Table legend) after drug or saline administration. Measurement in a dark room was used because it gave higher level of motility in the control groups, thereby increasing the sensitivity of an inhibition test. Inhibition of motility was calculated in percent of the response of a parallel control group. ED_{50} values were calculated by log-probit analysis. At least four rats were used in each dosage group, and at least eight rats were used in the control group.

Drugs

The following drugs were dissolved in saline: remoxipride hydrochloride (molecular weight (MW) 426; Astra Arcus, Sweden), Seroquel fumarate (MW 500; synthesized at Dept. Medicinal Chemistry, H. Lundbeck, Denmark), fluphenazine dihydrochloride (MW 510; Squibb, USA), cis(Z)-flupentixol dihydrochloride (MW 510; H. Lundbeck, Denmark), amperozide hydrochloride (MW 437; Kabi-Pharmacia, Sweden), mepyramine maleate (MW 401) and D-amphetamine hemisulphate

Table 1
Effect of classical, newer and potential antipsychotics on hypermotility induced by low (0.5 mg/kg) and high (2.0 mg/kg) doses of D-amphetamine (AMPH) in rats

Compound (treatment time before test, h)	ED_{50} (μmol/kg s.c.)		Ratio AMPH/ED_{50} values	ED_{50} (μmol/kg s.c.)
	AMPH 0.5	AMPH 2.0		Inhibition spontaneous locomotor activity
Newer antipsychotics				
Sertindole (2)	0.25 [b]	4.6	18	12 [d]
Clozapine (0.5)	1.2 [b]	12	10	7.8 [d]
Risperidone (2)	0.35 [b]	3.5	10	2.6
Olanzapine (2)	1.4 [a]	9.1	6.5	8.7
Ziprasidone (2)	0.47 [b]	5.7	12	12
Remoxipride (2)	2.9	4.8	1.7	> 47
Seroquel (2)	4.6 [c]	> 40	> 8.7	72
Amperozide (0.5)	2.6 [c]	> 46	> 18	34 [d]
MDL 100.151 (2)	0.64 [c]	> 13	> 25	> 54
Classical antipsychotics				
Haloperidol (2)	0.099 [b]	0.24	2.4	0.41 [d]
Fluphenazine (2)	0.029	0.026	0.90	0.092 [d]
Cis-(Z)-Flupentixol (2)	0.028	0.034	1.2	0.12

For comparison the inhibitory potencies of the same compounds on spontaneous locomotor activity are indicated. The compounds were injected 0.5 or 2 h before the start of motility testing. Each drug was studied in at least three dose levels. For further details, see Materials and methods. NT: not tested. [a] $P < 0.02$; [b] $P < 0.01$ indicate significantly higher potency compared with inhibition of D-amphetamine 2.0 mg/kg. [c] Indicates selective inhibition of D-amphetamine 0.5 mg/kg. [d] Indicates data published previously (Sánchez et al., 1991).

(both Nomeco, Denmark). The following drugs were dissolved by addition of minimum amounts of dilute acid (methane-sulphonic acid, tartaric acid, phosphoric acid, hydrochloric acid or acetic acid): Sertindole (MW 441; H. Lundbeck, Denmark), risperidone (MW 410), haloperidol (MW 376) and ritanserin (MW 478;

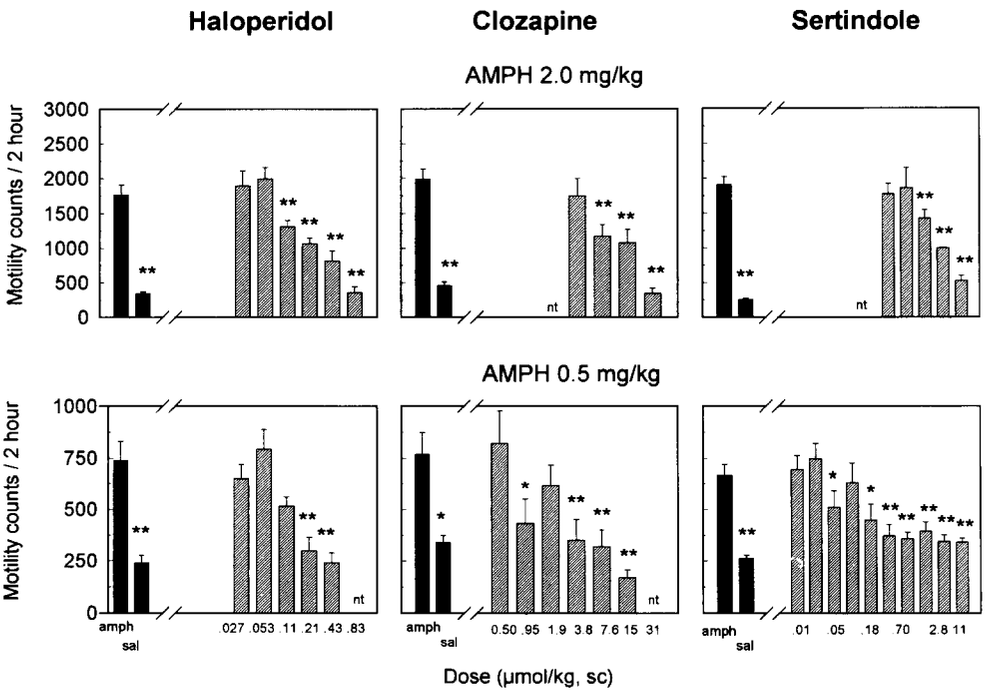

Fig. 1. Effect of haloperidol, clozapine and sertindole on hyperactivity induced by D-amphetamine (AMPH) 2.0 mg/kg (top) or 0.50 mg/kg (bottom). Test compound or vehicle was injected 0.5 (clozapine) or 2 h before s.c. administration of D-amphetamine or saline. The cumulated motility counts (mean ± S.E.M.) measured in a 2 h period are indicated for control groups receiving saline + D-amphetamine or saline + saline (sal; filled bars) and for the groups receiving test drug + D-amphetamine (hatched bars). Each group consists of at least seven rats. * $P < 0.05$ and ** $P < 0.01$, significant difference from D-amphetamine control group (one-way ANOVA followed by Bonferroni's t-test).

Janssen, Belgium), olanzapine (MW 315), ziprasidone (MW 413; propyleneglycol also added to dissolve the compund) and MDL 100.151 ((±)-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidine-methanol; MW 374). The three last mentioned compounds were synthesized at Dept. of Medicinal Chemistry, H. Lundbeck. Prazosin hydrochloride (MW 419; Pfizer, USA) was dissolved in deionized water. Injection volumes were 5 ml/kg body weight.

3. Results

3.1. General

A dose-dependent hypermotility was induced by D-amphetamine at dosages between 1.4 and 11 μmol/kg s.c. (0.25–2.0 mg/kg), whereas higher D-amphetamine dosages induced focussed stereotypies and less locomotor hyperactivity (data not shown). Two dose levels (0.5 and 2.0 mg/kg) were chosen for the subsequent studies of D-amphetamine inhibition as (1) the lowest dose inducing a robust increase in locomotor activity and (2) the dose inducing the maximum hypermotility, respectively.

3.2. Effect of established and putative antipsychotic drugs

The potencies of the test compounds are summarized as ED_{50} values in Table 1 and shown as dose-response curves for selected drugs (haloperidol, clozapine and sertindole) in Fig. 1. For comparison the ED_{50} values for inhibition of spontaneous locomotor activity in the absence of D-amphetamine are indicated in Table 1.

The classical antipsychotic drugs haloperidol, cis(Z)-flupentixol and fluphenazine have almost similar inhibitory effects on hypermotility induced by low and high dosage of D-amphetamine although the potency of haloperidol is significantly higher against D-amphetamine 0.5 mg/kg (Table 1; Fig. 1 for haloperidol). Inhibition of spontaneous locomotor activity is induced at dose levels slightly higher than those inhibiting the response to D-amphetamine 2.0 mg/kg (ED_{50} potency ratios of 1.7–4).

Newer and putative antipsychotics have a variable activity profile. The only common effect is that they all inhibit the response to D-amphetamine 0.5 mg/kg (Table 1).

Sertindole, clozapine, risperidone, olanzapine and ziprasidone preferentially inhibit the response to D-amphetamine 0.5 mg/kg with selectivity ratios to inhibition of D-amphetamine 2.0 mg/kg being 6.5–18 (Table 1; Fig. 1 for sertindole and clozapine). Spontaneous locomotor activity is inhibited by these compounds at dose levels similar to those inhibiting the response to the high (2.0 mg/kg) dose of D-amphetamine, sertindole and ziprasidone being the only exceptions by showing larger differentiation.

Remoxipride has a very different profile. It inhibits the response to both doses of D-amphetamine with similar potency, but does not inhibit spontaneous locomotor activity dose-dependently (Table 1).

Seroquel, amperozide and MDL 100.151 fail to block the response to D-amphetamine 2.0 mg/kg, while inhibiting that to D-amphetamine 0.5 mg/kg (Table 1). Accordingly, selectivity ratios cannot be determined quantitatively due to lack of parallellism of dose-response curves, but are larger than 9. Spontaneous locomotor activity is weakly or not affected by these compounds (Table 1).

3.3. Effect of selective neurotransmitter antagonists

The effects of the 5-HT_2 receptor antagonist ritanserin, the α_1-adrenoceptor antagonist prazosin and the histamine H_1 receptor antagonist mepyramine are shown as ED_{50} values in Table 2 and as dose-response relations in Fig. 2.

Ritanserin and prazosin inhibit the effect of D-amphetamine 0.5 mg/kg, whereas the response to D-amphetamine 2.0 mg/kg is inhibited only by prazosin,

Table 2
Effect of 5-HT_2, histamine H_1 and α_1-adrenoceptor antagonists on hypermotility induced by low (0.5 mg/kg) and high (2.0 mg/kg) doses of D-amphetamine (AMPH) rats

Compound (treatment time before test, h)	ED_{50} (μmol/kg s.c.)		Ratio AMPH/ED_{50} values	ED_{50} (μmol/kg s.c.)
	AMPH 0.5	AMPH 2.0		Inhibition spontaneous locomotor activity
Ritanserin (0.5)	1.8 [b]	> 5.2	> 2.9	> 21
Prazosin (2)	3.1 [a]	8.5	2.7	> 12
Mepyramine (0.5)	> 25	> 25	–	> 25

For comparison the inhibitory potencies of the same compounds on spontaneous locomotor activity are indicated. The compounds were injected 0.5 or 2 h before the start of motility testing. Each drug was studied in at least three dose levels. For further details, see Materials and methods. [a] $P < 0.01$ indicates significantly higher potency compared with inhibition of D-amphetamine 2.0 mg/kg. [b] Indicates selective inhibition of D-amphetamine 0.5 mg/kg.

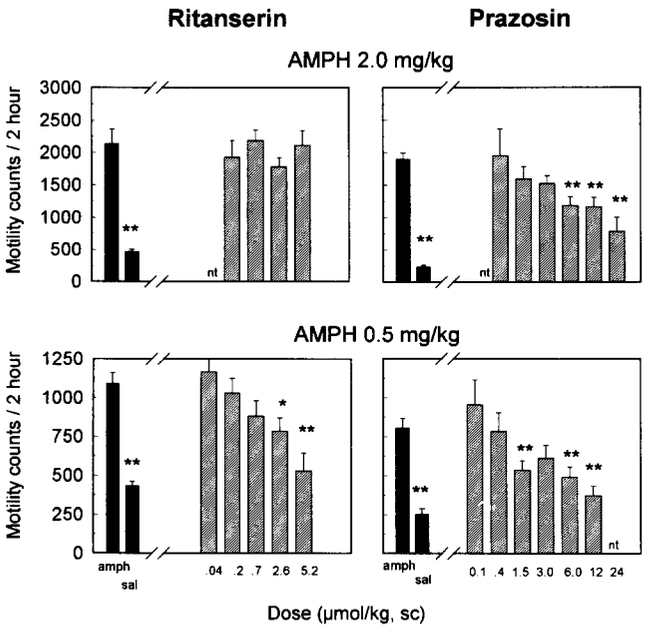

Fig. 2. Effect of ritanserin (30 min before test) and prazosin (2 h before test) on hyperactivity induced by D-amphetamine (AMPH) 2.0 mg/kg (top) or 0.50 mg/kg (bottom). The cumulated motility counts (mean ± S.E.M.) measured in a 2 h period are indicated for control groups receiving saline + D-amphetamine or saline + saline (sal; filled bars) and for the groups receiving test drug + D-amphetamine (hatched bars). Each group consists of at least seven rats. * $P < 0.05$ and * * $P < 0.01$, significant difference from D-amphetamine control group (one-way ANOVA followed by Bonferroni's t-test).

although prazosin is slightly more potent against D-amphetamine 0.5 mg/kg. Spontaneous locomotor activity is inhibited weakly by prazosin (Table 2); 42% inhibition is seen at 12 μmol/kg, accordingly, no ED_{50} value can be determined (data not shown).

Mepyramine inhibits neither D-amphetamine-induced nor spontaneous locomotor activity (Table 2).

4. Discussion

The results indicate that the receptor modulation of D-amphetamine-induced hyperactivity depends on the dose of D-amphetamine. It is well known that D-amphetamine-induced hyperactivity and stereotyped behaviour (induced by much larger doses of D-amphetamine) are mediated by different brain structures and have different pharmacology (cf. Introduction), but the demonstration that this is also so for hyperactivity induced by different doses of D-amphetamine in the absence of focussed stereotyped behaviour is new. It is not known whether different brain areas mediate the responses to high and low doses of D-amphetamine, but increases in dopamine function in different areas, e.g. nucleus accumbens, olfactory tubercle and frontal cortex have been shown to stimulate locomotor activity (Costall and Naylor, 1976; Cools et al., 1994; Blanc et al., 1994). If different brain regions are involved in the D-amphetamine-induced hyperactivity it is not surprising that the pharmacology of the responses differs. However, the hyperactivity may equally well be mediated within a single brain area in which neurotransmitter interactions differentially modulate the responses, depending on the dose of D-amphetamine and, accordingly, the induced change in dopamine activity in the area. Further studies are necessary to elucidate these questions.

It is obvious that dopamine D_2 receptor blockade is sufficient to inhibit D-amphetamine-induced hyperactivity at both dose levels with almost similar potencies. This is illustrated by the activity profiles of the classical antipsychotics haloperidol, fluphenazine and cis(Z)-flupentixol which preferentially block dopamine receptors in vivo (Hyttel et al., 1989; Leysen et al., 1993; Matsubara et al., 1993; Stockmeier et al., 1993) and by the benzamide derivative remoxipride which is a specific dopamine D_2 antagonist (Hall et al., 1986). The trend for increased inhibitory potency against D-amphetamine 0.5 mg/kg for three of the four compounds (although significant only for haloperidol) may simply be explained by the larger response of D-amphetamine needing more efficient receptor blockade to induce inhibition.

Furthermore, the results indicate that α_1-adrenoceptor antagonism can inhibit D-amphetamine-induced hyperactivity at both dose levels with a slight preference for inhibition of the effect of D-amphetamine 0.5 mg/kg. The involvement of α_1-adrenoceptors is a confirmation of earlier results (Rolinski and Scheel-Krüger, 1973; Snoddy and Tessel, 1985; Blanc et al., 1994). The mechanism behind this inhibitory effect may be dual: in addition to dopamine D-amphetamine is known also to release noradrenaline (Carr and Moore, 1970) which can contribute to induction of hyperactivity (Fishman et al., 1983; Svensson and Ahlenius, 1982) and secondly, recent experiments have demonstrated that blockade of α_1-adrenoceptors in the medial prefrontal cortex inhibits hyperactivity induced by intracerebral injection of D-amphetamine into nucleus accumbens, i.e. by an interaction between adrenergic and dopaminergic systems in two different brain areas (Blanc et al., 1994).

Blockade of 5-HT_2 receptors selectively antagonizes the effects of D-amphetamine 0.5 mg/kg, as illustrated by the activity profile of ritanserin (5-$HT_{2A/2C}$ receptor antagonist) and MDL 100.151 (5-HT_{2A} receptor antagonist). This is a qualitative rather than a quantitative difference in contrast to the results obtained with dopaminergic and α_1-adrenoceptor antagonists discussed above. This adds strong evidence that different mechanisms are involved. MDL 100.151 is a racemate of which the active enantiomer is MDL 100.907 (Soren-

sen et al., 1993). MDL 100.151 has also selective affinity for 5-HT_{2A} receptors in vitro (H. Lundbeck, unpublished observations). Furthermore, amperozide can be regarded as a functional 5-HT_2 receptor antagonist in vitro and in vivo (Sorensen et al., 1993; Leysen et al., 1993; Meltzer et al., 1992). However, amperozide has also been shown to inhibit D-amphetamine-induced dopamine release directly in microdialysis experiments (Ichikawa and Meltzer, 1992). The mechanism of the selective inhibitory effect of 5-HT_2 receptor antagonism on D-amphetamine-induced hypermotility is not understood. Inhibitory effects of MDL 100.907 have been described previously (Sorensen et al., 1993; Palfreyman et al., 1993), and it has been suggested on basis of biochemical evidence that 5-HT_2 receptor antagonism is operative only in conditions of increased dopamine function, since weak or no effects are seen on resting dopamine activity (for further discussion, see Palfreyman et al., 1993).

It has neither been clearly demonstrated that α_1-adrenoceptor antagonism nor 5-HT_2 receptor antagonism is sufficient for inducing antipsychotic activity, but it has been hypothesized that particularly 5-HT_2 receptor antagonism may add to the antipsychotic efficacy of a dopamine D_2 receptor antagonist and to lower the risk of extrapyramidal side effects (Meltzer and Nash, 1991). Also, changes in central nervous system adrenergic function in schizophrenia are suggested (Van Kammen and Kelley, 1991) which may contribute to the activity profile of clozapine (Baldessarini et al., 1992; Prinssen et al., 1994). Electrophysiological studies also suggest that blockade of either α_1-adrenoceptors or 5-HT_2 receptors preferentially modulates the activity patterns of mesolimbic dopamine neurones (Andersson et al., 1994; Svensson et al., 1995). Although the evidence is relatively weak it should be noted that some antipsychotic activity has been claimed for ritanserin (e.g. Wiesel et al., 1994). No convincing effect of α_1-adrenoceptor antagonist monotherapy has been documented but the possibility of obtaining receptor blockade in the central nervous system may be limited by peripheral side effects (e.g. hypotension). These speculations are important for the evaluation of the value of the D-amphetamine 0.5 mg/kg hypermotility model as a simple test for antipsychotic activity, particularly as to whether 5-HT_2 receptor antagonists and α_1-adrenoceptor blockers should be regarded as false positives in the test or whether insufficient clinical information is available.

The results of the present study are in agreement with these hypotheses. The newer antipsychotics which inhibit the hyperactivity induced by the low dose of D-amphetamine with higher selectivity indeed fulfill the criteria of having predominating 5-HT_2 receptor and/or α_1-adrenoceptor activity compared with dopamine D_2 receptor blockade in vivo. This includes clozapine ($\alpha_1 > 5\text{-}HT_2 > D_2$; Leysen et al., 1993; Arnt, 1992), sertindole ($5\text{-}HT_2 > \alpha_1 > D_2$; Domeney et al., 1994; Sánchez et al., 1991; Arnt, 1992), olanzapine ($5\text{-}HT_2 > D_2 = \alpha_1$; Moore et al., 1993), ziprasidone ($5\text{-}HT_2 > D_2 > \alpha_1$; Howard et al., 1994) and risperidone ($5\text{-}HT_2 > D_2 = \alpha_1$; Leysen et al., 1993; Megens et al., 1994). Seroquel (= ICI 204.636) which selectively inhibits the effect of D-amphetamine 0.5 mg/kg has preferential, but relatively weak, α_1-adrenoceptor blocking effect (Saller and Salama, 1993; Moore et al., 1993). The selectivity against D-amphetamine 0.5 mg/kg cannot be explained by its receptor profile.

In summary, the results indicate a complex regulation of D-amphetamine-induced hyperactivity, since it is modulated by several neurotransmitters, and has different pharmacological specificity at low and high doses, respectively. Further studies are in progress to further elucidate the relative importance of α_1-adrenoceptors, dopamine and 5-HT_2 receptors for inhibition of D-amphetamine-induced hyperactivity by use of combinations of selective compounds. Such studies may be of interest for development of antipsychotics with better separation between doses inducing antipsychotic and extrapyramidal side effects. Advantages over classical antipsychotics are demonstrated by clozapine (Baldessarini et al., 1992, for review) and are also suggested by recent controlled studies of sertindole (Martin et al., 1994), risperidone (Chouinard et al., 1993) and olanzapine (Harrison et al., 1994) in schizophrenic patients. More extensive clinical experience with these compounds may help to evaluate the relative importance of these neurotransmitter receptors for antipsychotic efficacy and extrapyramidal side effects.

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