ELSEVIER

European Journal of Pharmacology 281 (1995) 241–250

ejp

Effects of antipsychotics on cognitive behaviour in rats using the delayed non-match to position paradigm

Michael Didriksen *

Institute of Biological Psychiatry, Department of Psychopharmacology, St. Hans Hospital, DK-4000 Roskilde, Denmark

Received 19 December 1994; revised 12 April 1995; accepted 13 April 1995

Abstract

The acute effects of the dopamine D_1 receptor antagonist SCH 23390 [(*R*)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepin-7-ol] hemimaleat, the dopamine D_2 receptor antagonists raclopride and haloperidol, the compounds with mixed receptor profiles clozapine, risperidone and sertindole, the α_1-adrenoceptor antagonist prazosin and scopolamine were investigated in a delay-response task, a test for working memory, for rats. SCH 23390 induced a delay-dependent impairment of the performance. Raclopride, haloperidol, clozapine, and risperidone induced a delay-independent impairment. Sertindole was without effect. The specific (delay-dependent) and unspecific (delay-independent) effects on working memory of the dopamine D_1 and D_2 receptor antagonists, respectively, were associated with the dominance of dopamine D_1 receptors in the prefrontal cortex and of dopamine D_2 receptors in the basal structures of the brain. Prazosin did not affect working memory; however, a reduction in intertrial responses was found. Scopolamine induced a delay-independent impairment. It is concluded that the compounds have different activity profiles in this cognitive task. This finding may have important implications for the development of antipsychotics with a lower propensity for cognitive side effects.

Keywords: Antipsychotic; Cognition; Delay non-match to position; (Rat)

1. Introduction

In recent years, evidence has accumulated that schizophrenia is associated with deficits of various cognitive functions. A number of studies suggest that the deficits are associated with prominent dysfunction in the frontotemporal cortex (Park and Holzman, 1992; Goldberg et al., 1990; Weinberger et al., 1992). Deficits associated with the prefrontal cortex may be related to a decreased metabolic rate (Cohen et al., 1987; Weinberger and Berman, 1988).

Cognitive deficits are more likely to be associated with high negative symptom ratings than with positive symptoms (Addington et al., 1991). This is supported by the findings of Braff (1989), who showed that patients with an excess of negative symptoms showed reduced information processing relative to patients with predominating positive symptoms. Furthermore, in the Wisconsin Card Sorting Test, a test for working memory, patients with negative or mixed symptoms showed a higher mean number of perseverative errors than patients with positive symptoms. Negative symptoms are similar to many of the clinical manifestations of frontal lobe diseases (Weinberger, 1988).

Antipsychotic treatment is efficacious with regard to positive symptoms, whereas negative symptoms are only slightly affected. Due to the association between cognitive deficits related to prefrontal cortical activity and negative symptoms, it may be hypothesized that antipsychotic compounds, with beneficial effects on the performance of cognitive tasks dependent on the prefrontal cortex, may be beneficial in the treatment of negative symptoms as well. Antipsychotic compounds should preferably not impair cognition. In this study, the effects on cognitive behaviour of specific dopamine receptor antagonists and of classical and newer antipsychotic compounds are investigated. The prefrontal cortex is involved in the cognitive process of working memory (Owen et al., 1990; Sawaguchi and Goldman-

* Corresponding author. Pharmacological Research, H. Lundbeck A/S, Ottiliavej 7–9, DK 2500, Copenhagen-Valby, Denmark. Tel. +45 36301311, fax +45 36305267.

SSDI 0014-2999(95)00242-1

Rakic, 1991). Therefore, a visual-spatial model based on the delayed non-matching to position paradigm (Dunnett et al., 1988), a model for working memory, was used. The setup is based on the method described by Etherington et al. (1987). In the present study, only the delayed non-match to position task was used. The delayed non-match to position task produces a lower variance, provides higher levels of significance, and has been found to be advantageous compared to the delayed match to position task (Dunnett et al., 1988).

2. Materials and methods

2.1. Animals

Thirty-seven male Wistar rats and 40 male Long-Evans rats (Møllegaard Breeding Centre, Denmark) were used. The rats were food deprived to 80% of free feeding body weight, by adjusting their daily intake of laboratory chow; they were given 10 g laboratory chow (Altromine No. 1314) per day. The animals were housed in pairs, in a colony room at a constant temperature of 20° C, and humidity of 60–70%, with a 6:00 a.m. light/6:00 p.m. dark cycle. Tap water was available ad libitum. During the test period the age of the rats was 6–14 months.

2.2. Apparatus

Four aluminium and Perspex chambers (35.0 × 38.0 × 30.5 cm^3) with concave rear walls were used. In the concave wall were three holes (2.5 cm in diameter). They were 5 cm deep and placed 3.5 cm above the floor. The distance between the holes was 6.0 cm. Each hole was illuminated by a standard 1.5 W bulb placed at the bottom of the hole. On the opposite wall, a food tray (5.5 × 4.5 cm) was placed 2.0 cm above the floor. The food tray was covered by a hinged flap. A dipper delivered 0.1 ml of chocolate milk. A 3 W bulb was placed above the food tray. The bulb was turned on when the chocolate milk was accessible. The operant chambers were placed in sound-attenuated boxes of wood. Houselight was provided by a 5 W bulb placed centrally in the roof. The parameters measured were recorded automatically via an interface (Med Associates) to a personal computer (IBM compatible PC/AT, 80286).

2.3. Procedure

Shaping

The rats were introduced to the test in a graded series of stages. Three different 20 min procedures were used: (a) The rats were trained to collect the reward from the food tray. On the first session the panel flap was taped back. The chocolate milk was accessible in 15-s intervals. The rats continued on this procedure until they came to the panel 40 times. (b) The rats were trained to poke their nose in the illuminated hole for reward. The centre hole was illuminated until the rat responded. A response in the hole led to access to the chocolate milk for 5 s after the rat had entered the food tray. The rats continued on this procedure until they made 40 trials within a session. (c) This procedure consisted of steps 1–3 in Fig. 1. The rats had to achieve 85% correct responses before the following training program was introduced.

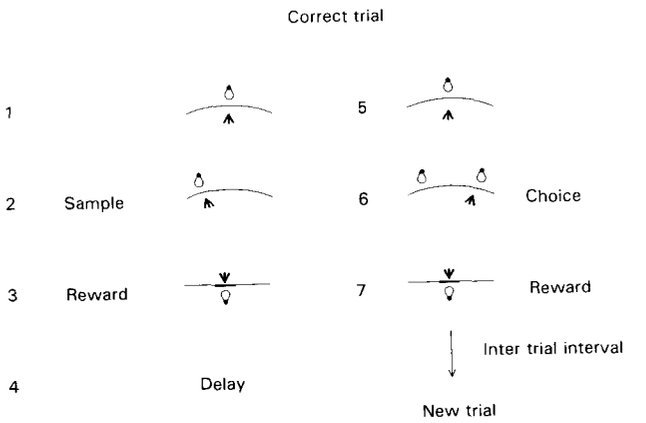

Fig. 1. Illustration of the seven stages of a correct trial. The curved lines represent the concave wall with the three holes. The bulb indicates where the stimulus is presented, and the arrows indicate correct responses. A correct response leads to extinction of the light. An incorrect response is registered when the rat responds to the unlit holes, panel or during the intertrial interval; responses during the delay period are allowed. An error response causes all lights to be extinguished for 2 s followed by an intertrial interval and a new trial.

Training

The task is illustrated in Fig. 1. The start of the session was signalled by the illumination of the house light. After a 5-s intertrial interval the centre hole was illuminated and a response in it caused the random illumination in one of the side-holes (sample stage). A response in the illuminated side-hole led to access to the chocolate milk at the front of the chamber for 2 s. Thus, the rats had to turn away from the holes in the rear of the chamber between the sample and choice stages. A response during the intertrial interval led to time-out, when all the lights in the box were turned off for 2 s. A new trial was then started by the illumination of the house light followed by an intertrial interval. A response in the unlit holes or the panel led to time-out.

Once the chocolate milk was collected, a response was again required in the illuminated centre hole and was followed by the illumination of both side-holes (choice stage). The rats were required to respond in the hole that had not been illuminated in the sample

stage. A response in any other hole or in the panel led to time-out, whereas a correct response led to access to the chocolate milk for 5 s. Collection of the chocolate milk led to the start of the next trial. The session continued for 20 min. Training was repeated until all rats had reached a criterion baseline performance of 85% correct responses.

The baseline schedule was subsequently altered to incorporate up to four different delays, randomly ordered within a single session. A delay was interposed between the collection of the chocolate milk after the sample stage and the illumination of the centre hole. Premature responses during the delay had no consequences. The delays were gradually inserted and increased to 9 s (8 s for scopolamine). The training continued until the rats attained an asymptotic level of performance.

The animals were ready for the test after approximately 80 sessions including shaping.

Test

The animals were divided into four groups ($n \geq 9$). The rats were tested Tuesday, Wednesday and Thursday. On Tuesday and Wednesday all animals received saline and Wednesday was regarded as the control session for the subsequent test session. On Thursday, three groups were treated with the compounds investigated and the fourth group received saline. The saline group was always the same. This group functioned as the control of baseline performance of the animals and for the comparability of the control versus the test session. In the subsequent week, the animals were run in the model again; however, the animals were not treated, and the week was regarded as a wash-out period.

2.4. Statistics and measures

The performance of each group on the control day and test day was compared by means of a 1- and 2-way analysis of variance (ANOVA) with day and delay as within-subject factors (Crunch statistical package, version 4).

In steps 1–5 (Fig. 1) the rat was guided through the test and responded only to one stimulus at a time. Normally, the animals performed this part of the task with nearly 100% correct responses. To evaluate the performance in this part of the test a parameter named 'index of unspecific performance' was derived:

$$\text{Index of unspecific performance} = \frac{\text{Correct response} - \text{Error response (step 1} - 5)}{\text{Correct response} + \text{Error response (step 1} - 5)}$$

The index of unspecific performance varies from +1 to −1. +1 indicates that the animal had responded correctly on all steps from 1–5, whereas an index of unspecific performance of −1 indicates that the animal had made an error response in *one* of the five steps and, therefore, never reached the choice stage.

The measures from the saline group are not presented in the results as the performance on the test day and control day never differed.

2.5. Drug treatments

SCH 23390 [(*R*)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepin-7-ol] hemimaleat (Schering, USA); raclopride [tartrate] (Astra, Sweden); haloperidol (Serenase 5 mg/ml, Janssen, Belgium); and scopolamine HBr were dissolved in 0.9% NaCl solution. Prazosin hydrochloride (Pfizer, Belgium) was dissolved in distilled water. Clozapine (Sandoz, Basel) was dissolved in 0.1 N HCl and diluted with distilled water (pH 6–7). Sertindole (Lundbeck, Denmark) was dissolved in 0.1 N HCl and diluted with 0.9% NaCl (pH 6). Risperidone (Janssen, Beerse) was dissolved in 0.4 M tartaric acid and diluted with 0.9% NaCl (pH 6). SCH 23390, raclopride, haloperidol, clozapine, risperidone, and scopolamine were injected in a volume of 1.0 ml/kg; prazosin and sertindole were injected in a volume of 4.0 ml/kg. The compounds were administered by subcutaneous injection 30 min before the test session. The highest dose (1.25 mg/kg) of sertindole was also tested 2 h after administration.

Two different strains of rats were used; SCH 23390, raclopride, and sertindole were tested in Long-Evans rats, whereas risperidone and prazosin were tested in Wistar rats. Haloperidol (0.02 mg/kg) and clozapine (0.63 and 1.25 mg/kg) were tested in Long-Evans rats, whereas haloperidol (0.01 mg/kg) was tested in Wistar rats. Furthermore, clozapine (2.5 mg/kg) and haloperidol (0.04 mg/kg) were tested in both strains of rats to ensure comparability of the drug effects between strains.

3. Results

3.1. Performance in choice stage

SCH 23390 (Fig. 2A) was without effect on performance in the choice stage at the two lower doses, whereas the high dose (0.02 mg/kg) suppressed the performance ($F(1,70) = 6.9$, $P < 0.05$). The 1-way ANOVA revealed a suppressing effect in delay 3 and 6.

Raclopride (Fig. 2B) only affected performance in the choice stage at the highest dose (0.08 mg/kg) ($F(1,70) = 18.0$, $P < 0.01$). The 1-way ANOVA showed a suppression of both the shortest and the longest

delays. A day × delay interaction was found ($F(3,70) = 3.1$, $P < 0.05$).

Haloperidol (0.01 mg/kg) (Fig. 3A) had no effect on choice accuracy. The 2-way ANOVA showed no significant effect of 0.02 mg/kg either; however, an interaction effect was found ($F(3,24) = 3.3$, $P < 0.05$). One-way ANOVA revealed a decreased performance in delay 9. Haloperidol (0.04 mg/kg) induced a delay-independent disruption of the performance independent of the rat strain used (Long-Evans (the data presented in Fig. 3A): $F(1.63) = 10.2$, $P < 0.05$; Wistar: $F(1,81) = 33.1$, $P < 0.05$ (data not presented)).

Clozapine (2.5 mg/kg) (Fig. 3B) suppressed the performance independently of the various delays in both strains of rats (Long-Evans (the data presented in Fig. 3B): $F(1,70) = 8.8$, $P < 0.05$; Wistar: $F(1,81) = 11.8$, $P < 0.05$ (data not presented)). A dose of 1.25 mg/kg induced suppression at delay 3; however, this effect was due to an unusually high level of performance at delay 3 on control day.

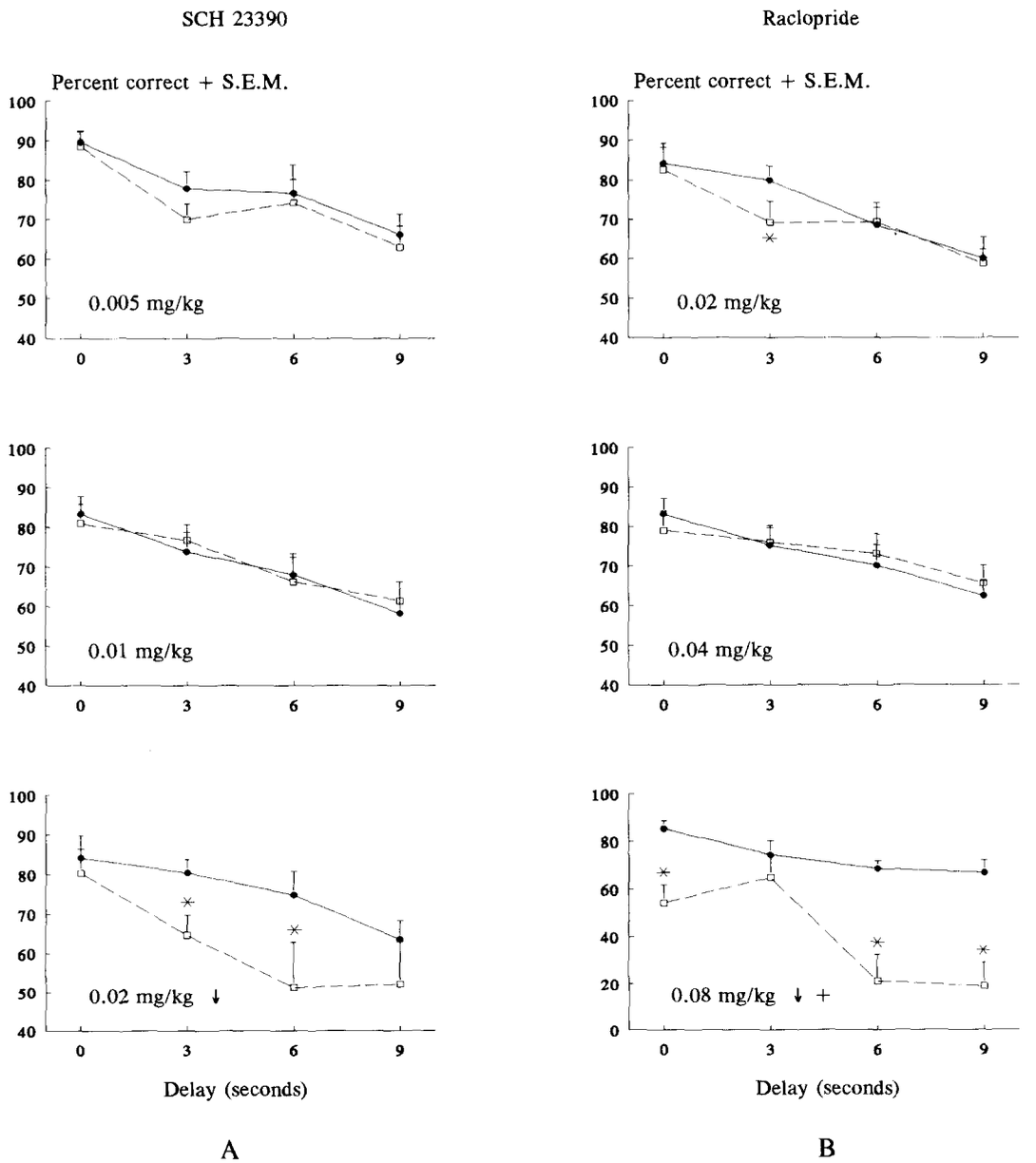

Fig. 2. Delayed non-match to position performance of rats following injection of SCH 23390 (A) or raclopride (B). The results are presented as means in percent + S.E.M. as a function of delays measured in seconds. $^{*}P < 0.05$ versus control day, by 1-way ANOVA with day as within factor. ↓ and + placed next to the dose tested indicate a significant decrease and a day × delay interaction, respectively, calculated by 2-way ANOVA with day and delay as within factors. ● Control day, □ test day.

Sertindole (Fig. 4A) in the two higher doses tested was without effect. A dose of 0.04 mg/kg improved performance in delay 3; however, this effect could be attributed to the unusually low level of performance on the control day. There was also no effect of the high dose (1.25 mg/kg) 2 h after administration ($F(1,63) = 1.4$, $P > 0.05$) (data not shown).

Risperidone (Fig. 4B) had no effect on the response accuracy at the two lower doses, whereas 0.4 mg/kg induced a marked delay-dependent decrease in choice accuracy ($F(1,63) = 50.9$, $P < 0.001$); day × delay interaction ($F(3,24) = 11.2$, $P < 0.001$). One-way ANOVA showed impairment at all delays.

Prazosin (Fig. 5A) had only minor effects on choice accuracy. The day × delay interaction for 1.0 mg/kg ($F(3,24) = 4.2$, $P < 0.05$) was due to an abnormally high control level at delay 6, whereas 2.0 mg/kg was ineffective ($F(1,63) = 2.6$, $P > 0.05$). However, a trend towards a delay-independent suppression of performance was evident.

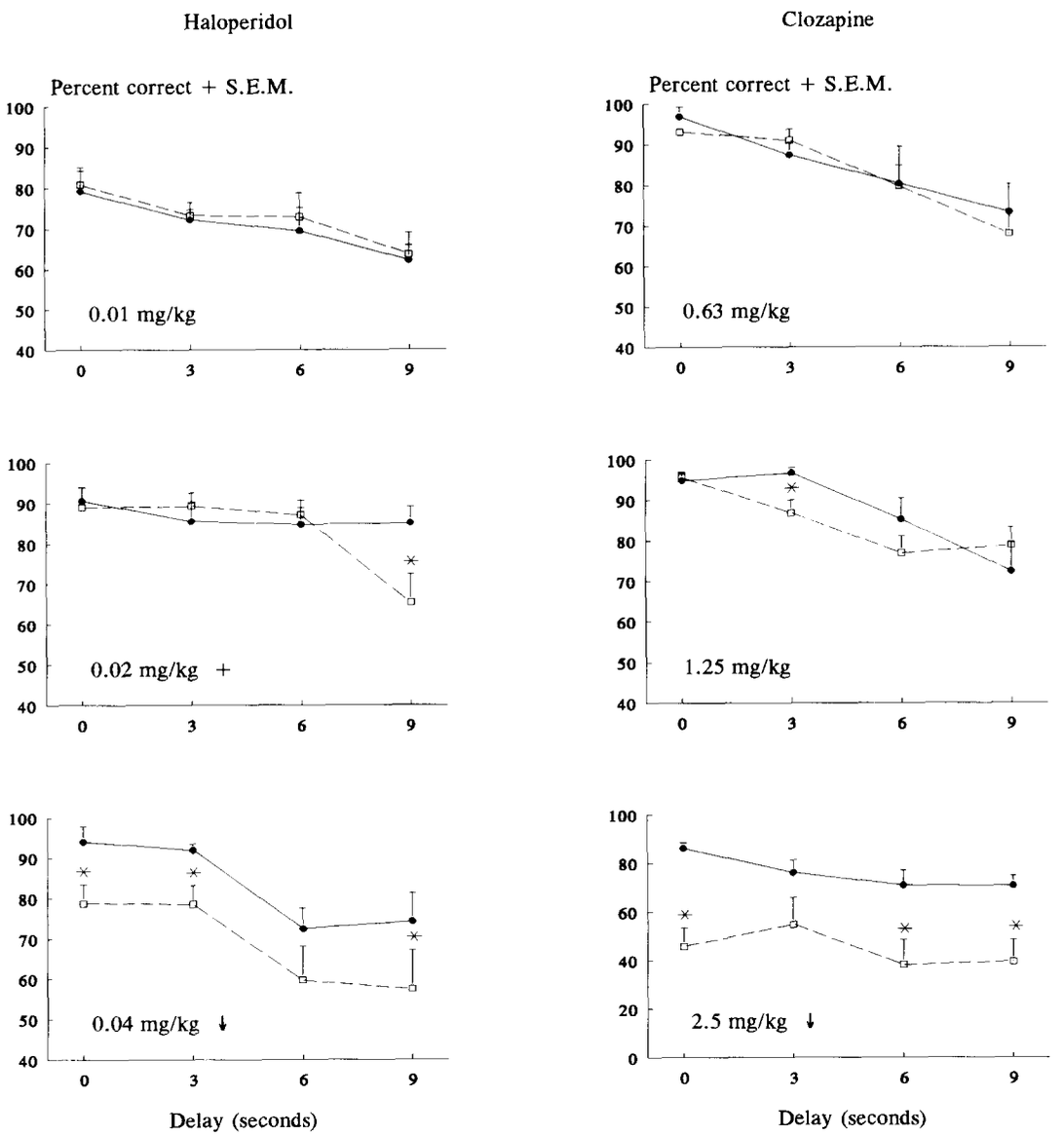

Fig. 3. Delayed non-match to position performance of rats following injection of haloperidol (A) or clozapine (B). The results are presented as means in percent + S.E.M. as a function of delays measured in seconds. $^{*}P < 0.05$ versus control day, by 1-way ANOVA with day as within factor. ↓ or + placed next to the dose tested indicate a significant decrease or a day × delay interaction, respectively, calculated by 2-way ANOVA with day and delay as within factors. ● Control day, □ test day.

Scopolamine (Fig. 5B) had only minor effects at the two lower doses. Although a 1-way ANOVA revealed a suppressing effect in the shortest delays, a day × delay interaction was found (0.04 mg/kg: $F(4,135) = 19.2$, $P < 0.001$; 0.08 mg/kg: $F(4,112) = 6.1$, $P < 0.001$). Scopolamine, at a dose of 0.16 mg/kg, induced a marked delay-independent disruption of the performance ($F(1,103) = 38.3$, $P < 0.001$); no day × delay interaction was found ($F(4,103) = 1.5$, $P > 0.05$).

3.2. Other parameters measured

The effect of the compounds on the number of trials, index of unspecific performance, and number of intertrial interval responses is summarized in Table 1. All compounds except sertindole suppressed the number of trials and the index of unspecific performance. The number of intertrial interval responses was not affected by raclopride, clozapine, and sertindole; how-

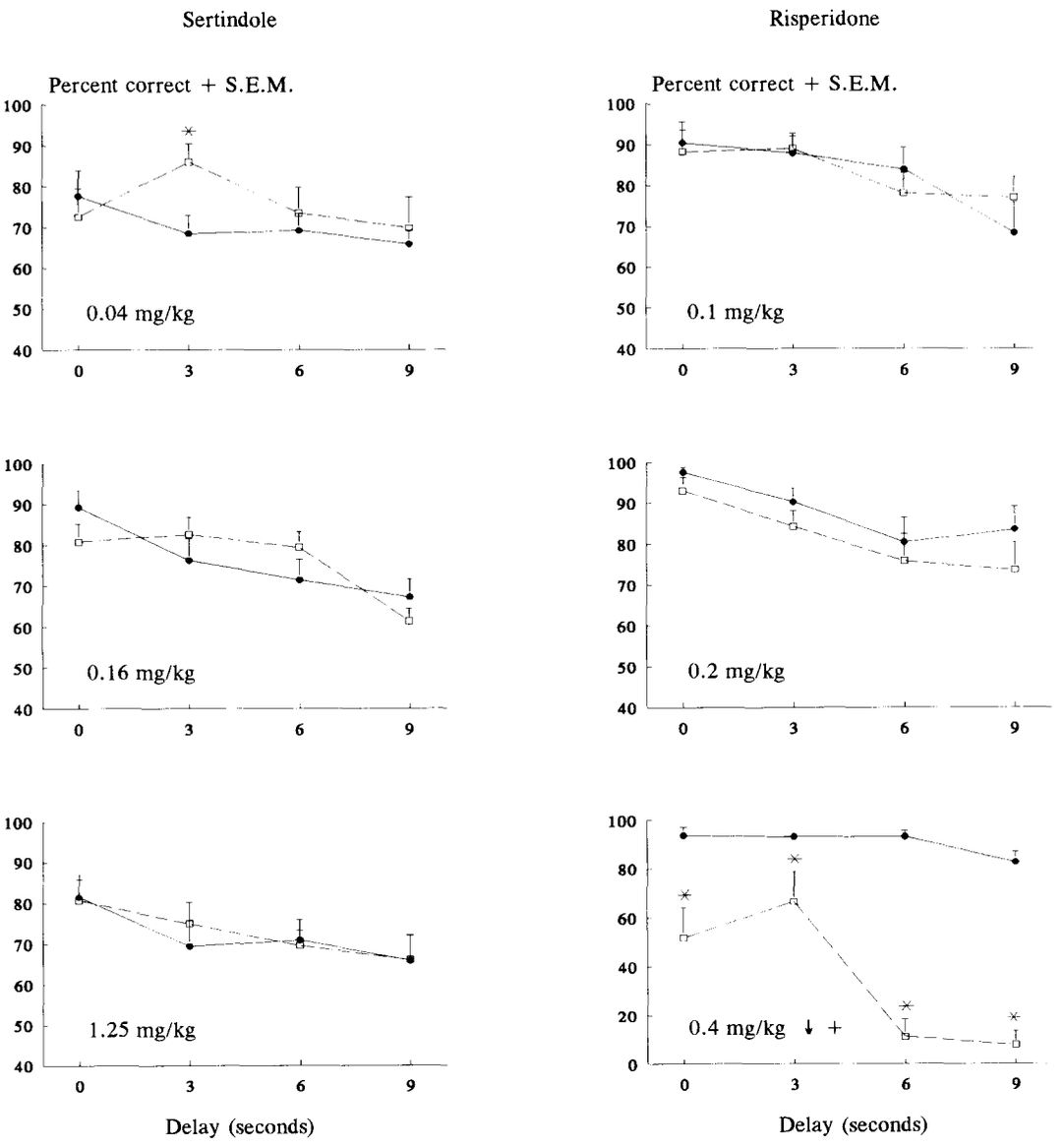

Fig. 4. Delayed non-match to position performance of rats following injection of sertindole (A) or risperidone (B). The results are presented as means in percent + S.E.M. as a function of delays measured in seconds. $^{*}P < 0.05$ versus control day, by 1-way ANOVA with day as within factor. ↓ and + placed next to the dose tested indicate a significant decrease and a day × delay interaction, respectively, calculated by 2-way ANOVA with day and delay as within factors. ● Control day, □ test day.

ever, a trend towards decreased activity was evident for raclopride, although this was not statistically significant due to a high standard deviation as a result of the marked effect of the compound.

4. Discussion

The main finding of this study was that all compounds tested, with the exception of sertindole, disrupted the performance of the task, suggesting that most, but not all, types of antipsychotic drugs disturb cognitive functioning in rats.

To ensure comparability of the drug effects between the two different strains of rats used, clozapine (2.5 mg/kg) and haloperidol (0.040 mg/kg) were tested in both strains. Overall, the effect of these two compounds in the two strains was comparable. Wistar rats compared to Long-Evans rats were slightly more sensitive to haloperidol but somewhat less sensitive to clozapine. Long-Evans rats were included in the study in order to investigate if the variability among rats was

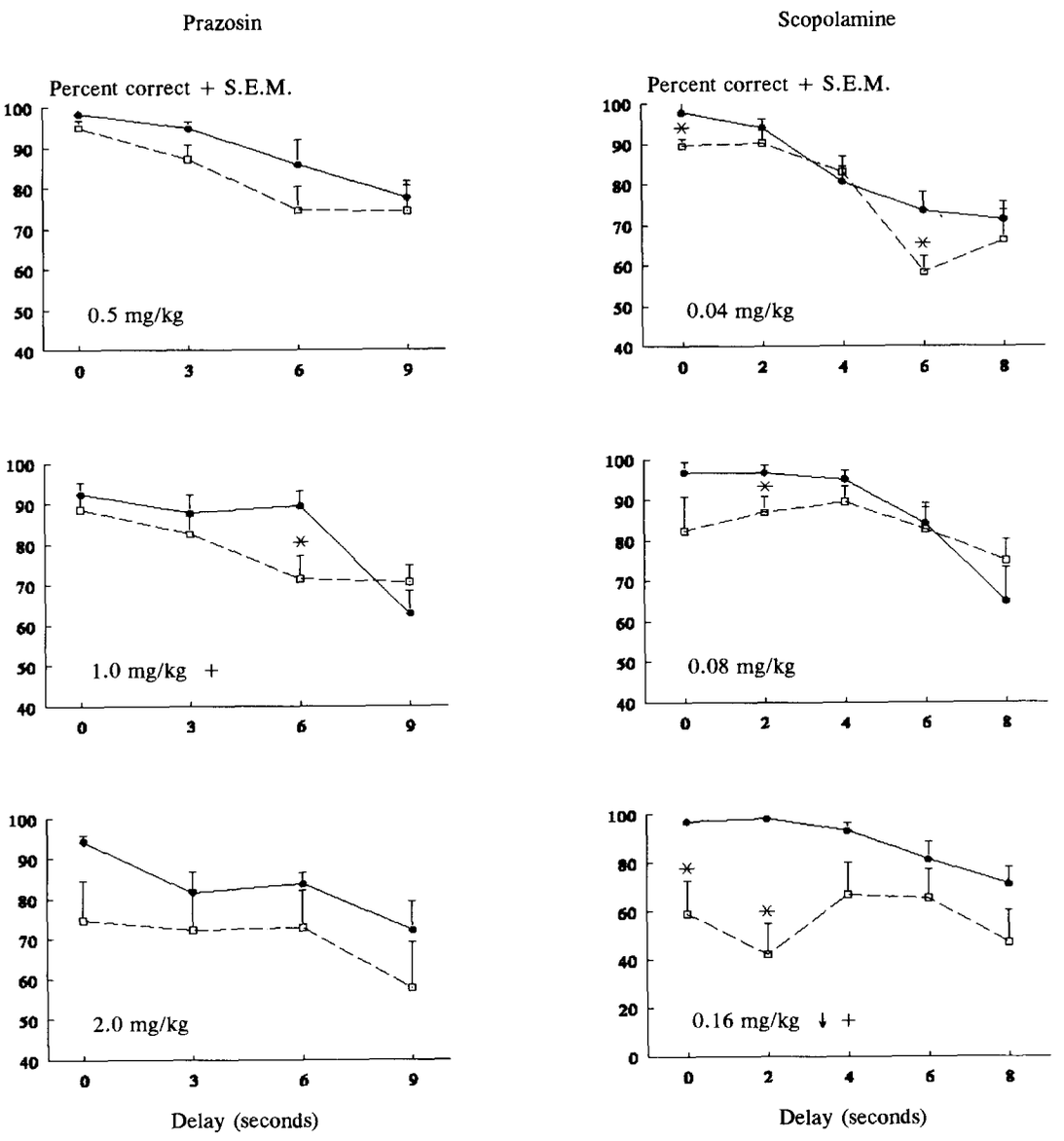

Fig. 5. Delayed non-match to position performance of rats following injection of prazosin (A) or scopolamine (B). The results are presented as means in percent + S.E.M. as a function of delays measured in seconds. $^{*}P < 0.05$ versus control day, by 1-way ANOVA with day as within factor. ↓ and + placed next to the dose tested indicate a significant decrease and a day × delay interaction, respectively, calculated by 2-way ANOVA with day and delay as within factors. ● Control day, □ test day.

smaller in an inbred strain. The variability among rats in the two strains was of the same magnitude. Consequently, in future studies Wistar rats will be used.

The effect of the compounds on the performance of the task depends on their receptor profile. Blockade of the dopamine D_1 receptor subtype by SCH 23390 induced a specific inhibition of working memory as the inhibition was delay dependent. Furthermore, a motor or motivational inhibition was induced, as indicated by the reduction in the number of trials and intertrial interval responses. The number of errors in steps 1–5 (Fig. 1) was slightly increased. The dopamine D_2 receptor antagonists raclopride and haloperidol disrupted the performance in the choice stage, independent of the delays selected. Moreover, all other parameters measured were reduced, especially the index of unspecific performance. The antipsychotics with mixed receptor profiles clozapine, sertindole, and risperidone affected the performance of the task differently. The effects of clozapine and risperidone were similar and comparable to the effects of the dopamine D_2 blocking compounds, while sertindole was ineffective. In vitro, sertindole has a high affinity for dopamine D_2 receptors (Sánchez et al., 1991); however, in acute in vivo tests for dopaminergic antagonism sertindole is remarkably weak or ineffective (Sánchez et al., 1991; Skarsfeldt, 1992). Another reason for the lack of effect of sertindole might be the relatively short time (30 min) between the injection and the testing of the compound. However, sertindole was also ineffective in the high dose 2 h after administration.

Clozapine, sertindole, and risperidone all block the 5-HT_2 receptor. Sertindole may be considered as a control for 5-HT_2 receptor blockade relative to dopamine D_2 receptor blockade since a 5-HT_2 antagonism occurs at doses well below those inhibiting

Table 1
Drug effects on trials, index of unspecific performance and intertrial interval responses

Parameter / Compound	Trials	Index of unspecific performance	Intertrial interval responses
Control range	51–59	0.62–0.88	11–30
SCH 23390			
0.005 mg/kg	57	0.85	13
0.01	53	0.77	12↓
0.02	28↓	0.59↓	4↓
Raclopride			
0.02 mg/kg	57	0.86	17
0.04	54	0.68	13
0.08	15↓	0.31↓	6
Haloperidol			
0.01 mg/kg	57	0.85	10
0.02	51↓	0.66	23
0.04 L	53↓	0.28↓	14↓
0.04 W	23↓	−0.01↓	7↓
Clozapine			
0.63 mg/kg	53	0.68	18
1.25	54	0.63	20
2.50 L	38↓	0.20↓	16
2.50 W	50	0.48↓	22
Sertindole			
0.04 mg/kg	55	0.74	12
0.16	58	0.86	9
1.25	58	0.90	8
Risperidone			
0.1 mg/kg	54	0.58	17
0.2	49	0.53↓	13
0.4	18↓	−0.15↓	5↓
Prazosin			
0.5 mg/kg	56	0.62↓	8↓
1.0	53	0.65	10↓
2.0	49	0.37	14↓
Scopolamine			
0.04 mg/kg	55	0.52	18
0.08	40↓	0.24↓	14
0.16	29↓	−0.37↓	9↓

Results are presented as the means from the test day. ↓ significant decrease versus control day for the respective group, by 1-way ANOVA with day as within factor. The control range is represented by the lowest and highest control values found. (L) Long-Evans, (W) Wistar.

dopaminergic or α_1-adrenergic mechanisms (Arnt, 1992; Hyttel et al., 1992). Thus, 5-HT_2 receptor antagonism seems not to have any consequences for the performance of this task, a conclusion supported by the results of Sawaguchi and Goldman-Rakic (1991). They showed that local injection of ketanserin, a 5-HT_2 receptor antagonist, into the prefrontal cortex was without effect in a spatial working memory task for monkeys.

Clozapine, sertindole, and risperidone all block the α_1-adrenoceptor. In order to exclude this effect as being responsible for the deficits, the α_1-adrenoceptor antagonist prazosin was studied. Prazosin did not affect working memory; however, a reduction in the intertrial interval responses was found without any reduction in the number of trials, possibly indicating a reduced impulsivity. It may be suggested that a decreased number of responses during the intertrial interval indicates an increased adaptation to the nature of the task as these responses are punished. If so, it would be reasonable to expect an improved performance. No improvement was found and it is not likely that such an effect was induced.

The differential effects of dopamine D_1 versus D_2 receptor antagonism were expected. The dopamine D_1 receptor is the predominating dopamine receptor subtype in the frontal cortex (for a review of dopamine and the regulation of prefrontal cortical function see Dolan and Grasby, 1994), whereas the dopamine D_2 receptor subtype is dominating in the hippocampus (Boyson et al., 1986) and more basal parts of the brain. The specific interference with working memory function induced by SCH 23390 may be related to the dominance of the dopamine D_1 receptor in the prefrontal cortex. This is supported by the findings of Sawaguchi and Goldman-Rakic (1991), who showed that local injection of SCH 23390 into the prefrontal cortex disrupted the performance of a spatial working memory task for monkeys. A similar effect was not found for either raclopride or ketanserin. The effect of the dopamine D_2 receptor blocking compounds may be mediated via the basal structures of the brain, e.g. the hippocampus, which is essential for cognitive functions (Squire et al., 1990). Furthermore, the memory-improving properties of dopamine receptor agonists on tasks sensitive to both hippocampal and caudate lesions are mediated via the dopamine D_2 receptor alone (Packard and White, 1989), or the dopamine D_1 and D_2 receptors in concert (Imperato et al., 1993; Packard and White, 1991). The effect of dopamine on cognitive functions via the hippocampus might be mediated through the action of dopamine on the release of acetylcholine (Imperato et al., 1993). The findings of Imperato et al. (1993) suggest that emotional and motivational drives, mediated by enhanced dopaminergic transmission, may lead to potentiation of attention and cognition. A reduction in motivational drive and attention may account for the reduced activity and index of unspecific performance, respectively, induced by the dopamine D_2 receptor blockers. The effects of risperidone and clozapine may be attributed to their effects on the dopamine D_2 receptor. Clozapine blocks the dopamine D_1 receptor to the same degree as the dopamine D_2 receptor (Farde et al., 1989) and the dopamine D_1 effect may be superimposed on the dopamine D_2 effect. However, the affinity of clozapine for dopamine D_1 and D_2 receptors is relatively small compared to its affinity for muscarinic receptors (Fitton and Heel, 1990). Therefore, the anticholinergic profile of clozapine might be the main reason for its effect since the profile of scopolamine in the present test and that of clozapine are comparable. This is supported by the work of Goldberg et al. (1993), who reported that antipsychotic treatment with clozapine is associated with a decline in some memory functions, an effect that is assigned to anticholinergic properties. Another possibility might be a combination of all the effects of clozapine. The lack of response of sertindole is in agreement with the lack of acute antidopaminergic action in vivo (Sánchez et al., 1991; Skarsfeldt, 1992). There is no ready explanation for why the α_1-adrenoceptor antagonistic action alone as well as the relative affinities for 5-HT_2 receptors, α_1-adrenoceptors and dopamine D_2 receptors of sertindole do not contribute to an inhibitory effect. The relative affinities might in fact be responsible for the lack of effect.

Most of the compounds tested in the present study have been tested in comparable doses in the Morris water maze (Scheel-Krüger, 1992), another animal model of cognitive function. In the water maze, SCH 23390, raclopride, and haloperidol also induced an impairment of performance, whereas sertindole was without effect. However, clozapine induced no disturbances at high dose levels (5–7.5 mg/kg), but rather an improvement after low doses (1–2.5 mg/kg), contrary to the present findings. Placing the animals in the water maze is far more stressful than placing the animals in the present test equipment and, accordingly, the initial induced stress may overcome a 'behavioural' blockade induced by the compound. In this case, clozapine does not disrupt the memory function but rather induces an initiation problem. The discrepancy between the tests demonstrates the importance of using several behavioural models when elucidating the activity profiles of drugs.

Improvement of psychiatric symptoms is not associated with major improvement of cognitive functions (Addington et al., 1991; Goldberg et al., 1993). This is not surprising based on the present results. The efficacy of antipsychotic treatment is mainly attributed to the improvement of positive rather than negative symptoms. Addington et al. (1991) found that cognitive

deficits were more likely to be associated with high negative symptom ratings than with positive symptoms. Since negative symptoms may associate with decreased dopaminergic transmission (Kay and Sandyk, 1991), a further dopaminergic blockade is unlikely to improve cognitive function. Moreover, dopaminergic facilitation by amphetamine has been shown to improve performance on the Wisconsin Card Sorting Test, a test for working memory, in schizophrenic patients (Daniel et al., 1991). These findings support the hypothesis that dysfunction of mesocortical monoaminergic activity is related to 'hypofrontality' in schizophrenia. Taken together, a blockade of dopaminergic transmission by antipsychotic compounds may not benefit schizophrenic patients with negative symptoms or cognitive deficits. Alternative treatment strategies should be considered.

Acknowledgements

I thank Jørgen Kring and Gertie Ward for technical assistance and the Lundbeck Foundation and Oda and Hans Svenningsens Fund for financial support.

References

Addington, J., D. Addington and E. Maticka-Tyndale, 1991, Cognitive functioning and positive and negative symptoms in schizophrenia, Schizophr. Res. 5, 123.

Arnt, J., 1992, Sertindole and several antipsychotic drugs differentially inhibit the discriminative stimulus effects of amphetamine, LSD and St 587 in rats, Behav. Pharmacol. 3, 11.

Boyson, S.J., P. McGonigle and P.B. Molinoff, 1986, Quantitative autoradiographic localization of the D_1 and D_2 subtypes of dopamine receptors in rat brain, J. Neurosci. 6, 3177.

Braff, D.L., 1989, Sensory input deficits and negative symptoms in schizophrenic patients, Am. J. Psychiatry 146, 1006.

Cohen, R.M., W.E. Sempel, M. Gross, T.E. Nordahl, L.E. DeLisi, H.H. Holcomb, A.C. King, J.M. Morihisa and D. Pickar, 1987, Dysfunction in a prefrontal substrate of sustained attention in schizophrenia, Life Sci. 40, 2031.

Daniel, D.G., D.R. Weinberger, D.W. Jones, J.R. Zigun, R. Coppola, S. Handel, L.B. Bigelow, T.E. Goldberg, K.F. Berman and J.E. Kleinman, 1991, The effect of amphetamine on regional cerebral blood flow during cognitive activation in schizophrenia, J. Neurosci. 11, 1907.

Dolan, R.J. and P.M. Grasby, 1994, Exploring the functional role of monoaminergic neurotransmission. A method for exploring neurotransmitter dysfunction in psychiatric disorders, Br. J. Psychiatry 164, 575.

Dunnett, S.B., J.L. Evenden and S.D. Iversen, 1988, Delay-dependent short-term memory deficits in aged rats, Psychopharmacology 96, 174.

Etherington, R., G. Mittleman and T.W. Robbins, 1987, Comparative effects of nucleus basalis and fimbria-fornix lesions on delayed matching and alternation tests of memory, Neurosci. Res. Commun. 1, 135.

Farde, L., F.A. Wiesel, A.-L. Nordström and G. Sedvall, 1989, D_1- and D_2-dopamine receptor occupancy during treatment with conventional and atypical neuroleptics, Psychopharmacology 99, S28.

Fitton, A. and R.C. Heel, 1990, Clozapine, a review of its pharmacological properties, and therapeutic use in schizophrenia, Drugs 40(5), 722.

Goldberg, T.E., D. Ragland, E.F. Torrey, J.M. Gold, L.B. Bigelow and D.R. Weinberger, 1990, Neuropsychological assessment of monozygotic twins discordant for schizophrenia, Arch. Gen. Psychiatry 47, 1066.

Goldberg, T.E., R.D. Greenberg, S.J. Griffin, J.M. Gold, J.E. Kleinman, D. Pickar, S.C. Schulz and D.R. Weinberger, 1993, The effect of clozapine on cognition and psychiatric symptoms in patients with schizophrenia, Br. J. Psychiatry 162, 43.

Hyttel, J., J.B. Nielsen and G. Nowak, 1992, The acute effect of sertindole on brain 5-HT_2, D_2 and α_1 receptors (ex vivo radioreceptor binding studies), 89, 61.

Imperato, A., M.C. Obinu and G.L. Gessa, 1993, Effects of cocaine and amphetamine on acetylcholine release in the hippocampus and caudate nucleus, Eur. J. Pharmacol. 238, 377.

Kay, S.R. and R. Sandyk, 1991, Experimental models of schizophrenia, Int. J. Neurosci. 58, 69.

Owen, A.M., J.J. Downes, B.J. Sahakian, C.E. Polkey and T.W. Robbins, 1990, Planning and spatial working memory following frontal lobe lesions in man, Neuropsychologia 28(10), 1021.

Packard, M.G. and N.M. White, 1989, Memory facilitation produced by dopamine agonists: role of receptor subtype and mnemonic requirements, Pharmacol. Biochem. Behav. 33, 511.

Packard, M.G. and N.M. White, 1991, Dissociation of hippocampus and caudate nucleus memory systems by posttraining intracerebral injection of dopamine agonists, Behav. Neurosci. 105, 295.

Park, S. and P.Z. Holzman, 1992, Schizophrenics show spatial working memory deficits, Arch. Gen. Psychiatry 49, 975.

Sánchez, C., J. Arnt, N. Dragsted, J. Hyttel, H.L. Lembøl, E. Meier and T. Skarsfeldt, 1991, Neurochemical and in vivo pharmacological profile of sertindole, a limbic-selective neuroleptic compound, Drug Dev. Res. 22, 239.

Sawaguchi, T. and P.S. Goldman-Rakic, 1991, D_1 dopamine receptors in prefrontal cortex: involvement in working memory, Science 251, 947.

Scheel-Krüger, J., 1992, Comparison of typical and atypical neuroleptics in the Morris Swim Maze, Behav. Pharmacol. 3(S1), 18.

Skarsfeldt, T., 1992, Electrophysiological profile of the new atypical neuroleptic, sertindole, on midbrain dopamine neurones in rats: acute and repeated treatment, Synapse 10(1), 25.

Squire, L.R., S. Zola-Morgan, C.B. Cave, F. Haist, G. Musen and W.A. Suzuki, 1990, Memory: organization of brain systems and cognition, Cold Spring Harbor Symp. Quant. Biol. 55, 1007.

Weinberger, D.R., 1988, Schizophrenia and the frontal lobe, Trends Neurosci. 11, 367.

Weinberger, D.R. and K.F. Berman, 1988, Speculation on the meaning of cerebral metabolic hypofrontality in schizophrenia, Schizophr. Bull. 14, 157.

Weinberger, D.R., K.F. Berman, R. Suddath and E.F. Torrey, 1992, Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: a magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins, Am. J. Psychiatry 149, 890.