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Comparison of the effects of antipsychotics on a delayed radial maze task in the rat

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Abstract *Rationale:* The cognitive impairments evident in many schizophrenics are related to the severity of their negative symptoms and ability to function in society. Drugs that alleviate cognitive impairments, in addition to other psychotic symptoms, may have an important influence on treatment outcome and the course of the illness. *Objectives:* A delayed non-match to sample task conducted in an eight-arm radial maze was used to determine the influence of four atypical antipsychotics (olanzapine, ziprasidone, risperidone, and clozapine), as well as a typical neuroleptic (haloperidol) on consolidation processes in healthy rats. *Method:* Well-trained rats were required to recall after a 7-h delay where they had received food pellets during an information phase (first four arm choices) in order to obtain the remaining food pellets during a retention phase (second four arm choices). *Results:* The total number of errors that occurred during the retention session increased with increasing delay periods from 0 to 7 h. When administered orally immediately after the information phase, olanzapine (3 and 5 mg/kg) and risperidone (0.1 mg/kg) significantly reduced the number of errors made during the retention phase. Under the same conditions, clozapine, ziprasidone and haloperidol failed to affect the total number of retention phase errors. *Conclusion:* Some atypical antipsychotics, such as olanzapine and risperidone, improve consolidation processes and may alleviate the cognitive impairments associated with schizophrenia.

Keywords Olanzapine · Atypical antipsychotics · Radial arm maze · Cognition

Introduction

Many schizophrenic patients exhibit impairments in attention, memory and executive function (for review, see Tollefson 1996), as well as prominent positive (e.g. delusions, hallucinations, and disorganization) and negative (e.g. affective flattening, anhedonia, anergia) psychotic symptoms. Cognitive deficits tend to occur early in the course of the illness and their severity can be predictive of the long-term treatment outlook for these patients (Green 1996). Although neuroleptics, such as haloperidol, may effectively treat the positive symptoms of schizophrenia, significant cognitive deficits remain (Spohn and Strauss 1989). In contrast, recent clinical evidence suggests that atypical antipsychotics, such as clozapine, risperidone and olanzapine, improve some domains of cognitive functioning, although there may be important differences in their clinical profiles (for review, see Meltzer and McGurk 1999). For instance, Purdon et al. (2000) found that treatment with olanzapine significantly improved immediate recall, a benefit that was not evident after treatment with risperidone or haloperidol.

The delayed non-match to sample (DNMS) task has been used successfully to study the effect of drugs on memory enhancement or impairment (Staubli et al. 1994; Pussinen and Sirvio 1999). In the radial maze version of this task, well-trained rats must recall where they received rewards during an information phase in order to obtain the remaining rewards during a retention phase conducted after a delay of several hours. Performance of this task is dependent upon the length of time the information must be retained and by the administration of putative amnesics and cognitive enhancers (Staubli et al. 1994; Pilcher et al. 1997; Pussinen and Sirvio 1999). A major advantage of this paradigm is that both memory enhancement and impairment by drugs can be studied without having to resort to lesioning animals, surgical procedures, or the use of amnesic challenges. Also, since testing occurs using food presentation as the motivating event, the inference can be made that the effects on memory are occurring at doses that do not behaviorally impair the animal.

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In the DNTS radial maze task, the total number of errors would be expected to increase with increasing delay periods between the information and retention phases. The decline in accuracy is characteristic of memory—forgetting occurs as a function of increased time. The time span over which spatial information may be retained depends on many factors such as the training schedule and the order of delay testing (e.g. Strijkstra and Bolhuis 1987; Markowska et al. 1983). Therefore, the number of errors that occurred after various delay intervals was determined first in order to find a suitable period at which to test for cognitive enhancing effects. Once a suitable delay interval had been selected, olanzapine, clozapine, risperidone and ziprasidone were studied. These results were compared to those obtained with a classical neuroleptic, haloperidol. All drugs were administered immediately after the information phase in order to determine their effect on memory consolidation without influencing either acquisition or retrieval processes.

Materials and methods

Subjects

Thirty adult, male Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, Ind., USA) were individually housed and maintained on a 12-h light-dark cycle (lights on at 6 a.m.). All testing was conducted at the same time each day during the light phase of the cycle. The rats had free access to water and were maintained at 85% of their free-feeding weight by supplemental feedings of Lab Diet #5001 for rodents (PMI Nutrition International Inc., St Louis, Mo., USA). Prior to the initiation of the present study, 17 of the subjects had previously been tested in the radial arm maze with unrelated compounds (5-HT or AMPA selective) and had at least a 1-month washout period during which no drugs were administered. This study was carried out in accordance with the policies set forth in the Guide for the Care and Use of Laboratory Animals (NIH).

Apparatus

The radial arm maze consisted of an octagonal platform (approximately 9 cm across each bay) from which eight symmetrically placed arms (approximately 9×70 cm) radiated (Habitest; Coulbourn Instruments, Allentown, Pa., USA). The arms were constructed of clear Plexiglas and were separated from the central platform by guillotine doors that were raised and lowered by computer (L2T2S control software; Coulbourn Instruments). Hoppers placed at the end of each arm delivered a single food reward (45 mg pellet; BioServ, Frenchtown, N.J., USA) at the beginning of each session. In order to count as an arm entry, the rat was required to run all of the way to the end of the alley and to cross a photobeam located at the opening of the food magazine. Arms were never re-baited within the same session.

Initial maze training

The rats were initially trained to search for food at the end of each of the eight arms. The rats were placed on the central platform with access to all of the arms blocked. The guillotine doors were raised and the rat was allowed to freely explore the maze. Each session continued until the rat had fully entered each alley and retrieved the food reward, or until 5 min (first two trials: 15 min) elapsed. Only the initial visit to an arm was reinforced. Once the rats had reached

the criteria of no more than two errors (i.e. entering the same arm more than once during a session) on 3 consecutive days, delay training was begun.

At the start of each delay trial, the rat was placed on the central platform with access to all of the alleys blocked. Four arms were randomly selected and baited with food. At the start of the trial, only the gates of the baited alleys were raised. This information phase lasted until all four alleys had been entered or until 5 min elapsed. The rat was removed from the last alley entered and placed back on the center platform. One minute later, the retention phase began. The four previously blocked alleys were baited, and all eight of the guillotine doors were raised. The rat was allowed to freely explore the maze until the four remaining pieces of food had been retrieved or until 5 min elapsed. Only the initial visit to a baited arm was rewarded each day. During the retention phase, any entry into an arm that had been baited during the information phase or re-entry into one of the arms baited during the retention phase was counted as an error. Once stable performance had been obtained (i.e. no more than one error was made on 3 consecutive days), other testing commenced. One training trial was given per day, Monday to Friday.

Influence of delay period

Ten rats were tested using the following delay periods between the information and retention phases: 0 min, 1 min, 30 min, 3 h, 7 h, and 24 h. Each rat was tested once in ascending delay order and once in descending order. The results were then averaged for each rat. In addition, random performance during the retention session was tested twice in each rat by omitting the information session (i.e. rats were placed in the maze but no gates were raised) and then testing the rats 24 h later in a “normal” retention session. No drugs were administered during any of these sessions.

Drug tests

All drug tests were conducted as described above using the 7-h delay period between the information and retention phases. At the conclusion of the information phase, the rat was removed from the maze, orally administered vehicle or various doses of the test drug, and placed back in its home cage for the 7-h delay. Each drug was tested in a range of doses known to be effective in other paradigms (Moore 1999). A novel set of arms was baited each day for each rat and the maze was thoroughly cleaned with a 70% isopropyl alcohol solution during the delay period. Drug or vehicle tests were conducted on Tuesday and Friday. The animals were not tested on the intervening days. Each rat received one or two of the antipsychotic drugs. All of the doses of any particular drug were administered in a semi-random order. Groups were balanced with respect to the weight of the rats and prior drug experience. The order of testing for each rat may be found in Table I. Appropriate baseline responding (using the 7-h delay between information and retention phases) was always obtained prior to initiating each drug test.

Data analysis

The data are expressed as the mean number of errors that occurred during the retention phase (\pm SEM). The statistical significance of the drug trials was determined using a repeated measure ANOVA followed by a Dunnett's test for comparison with control. The number of errors that were committed during the determination of each dose response curve was always compared to the average number of errors from one vehicle test conducted before drug dosing began and one test made after all the doses of that drug had been administered. This ensured that any reduction in the number of errors was due to a drug effect and not to a shift in the baseline number of errors. In order to obtain a baseline from which an improvement in cognition could be detected, a criterion was set

Table 1 Experimental history of rats. Y or N indicates an unrelated prior drug test

Rat no.	Preliminary data	Drug history	First test	Second test
1	Parametric	Y	Olanzapine	Ziprasidone
2	Parametric	Y	Risperidone ^a	–
3	Parametric	N	Haloperidol	–
4	Parametric	Y	Olanzapine ^a	–
5	Parametric	N	Haloperidol	–
6	Parametric	Y	Ziprasidone ^a	–
7	Parametric	Y	Haloperidol	–
8	–	Y	Risperidone	–
9	–	Y	Haloperidol	–
10	–	Y	Risperidone	Clozapine ^a
11	–	N	Olanzapine	Ziprasidone
12	–	Y	Olanzapine	Haloperidol
13	–	Y	Olanzapine ^a	–
14	–	Y	Olanzapine	Risperidone
15	–	Y	Olanzapine ^a	–
16	–	N	Olanzapine	Haloperidol ^a
17	–	N	Ziprasidone	Clozapine ^a
18	–	Y	Ziprasidone	–
19	–	N	Olanzapine	–
20	–	Y	Risperidone	Clozapine
21	–	Y	Risperidone	–
22	–	N	Clozapine	–
23	–	N	Risperidone	Clozapine
24	–	N	Ziprasidone ^a	–
25	–	N	Haloperidol ^a	–
26	–	Y	Ziprasidone	Clozapine
27	–	N	Ziprasidone	Clozapine
28	–	N	Risperidone	Clozapine
29	–	N	Haloperidol	–
30	–	Y	Haloperidol	–

^aData eliminated from analysis because rat failed to meet criteria of >2 errors on each of 2 vehicle control sessions

such that each rat was required to make at least two errors during each of the vehicle control sessions. If the rat failed to reach criterion, all of that rat's data was excluded from the statistical analysis. Over the course of the experiment, nine rats (one or two per drug study; see Table 1) were eliminated for this reason. Once a rat had been excluded from a drug study, it was no longer used in this paradigm. The latency and the total time taken to complete the maze during the information and retention phases were also recorded and analyzed in the same manner as the errors.

Drugs

Olanzapine, risperidone, ziprasidone, clozapine and haloperidol were dissolved in sterile water with the addition of a drop or two of lactic acid as needed. Both vehicle and drugs were administered by oral gavage in a volume of 1 ml/kg. Clozapine, risperidone and haloperidol were purchased from Sigma-Aldrich (St Louis, Mo., USA). Olanzapine and ziprasidone were supplied by Eli Lilly and Co. (Indianapolis, Ind., USA).

Results

Influence of delay period

An average of 12.7 (±0.6) days was required for the rats to reach criteria during the initial training on the simple eight-arm task. An additional 8.1 (±0.5) days of training

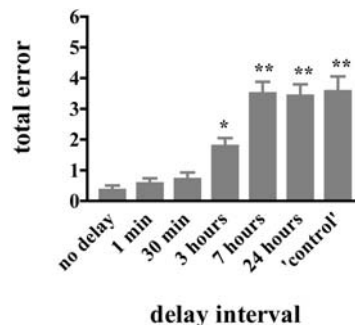


Fig. 1 Average number of errors committed during the retention session after various delay intervals. Each rat was tested twice after each delay and the results were averaged. In the “control” condition, the gates were not actually opened during the information session, so no information was available to the rat as to which alleys would be baited during the retention session. * Different from 0 and 1-min conditions, as well as 7-h, 24-h, and “control” conditions; $P < 0.05$. ** Different from no delay, 1 min, 30 min; $P < 0.05$. Error bars indicate the SEM; $n = 7$

were conducted using the 1-min delay between the information and retention phases.

The number of errors that occurred during the retention phase increased as the length of the delay period increased [one-way ANOVA: $F(6,36) = 25.48$; $P < 0.0001$; Fig. 1]. Although there were no differences after delays of 0 or 30 min, a 3-h delay significantly increased the number of errors (Tukey's multiple comparison test). The number of errors increased further after 7 h. However, increasing the delay to 24 h did not result in more errors than the 7-h delay. Neither the 7-h nor the 24-h delay condition differed from the “control” situation, in which no information had been given as to which alleys were baited. There were no significant differences in the latencies to begin or in the times required to complete the maze. Because 7 h delay between information and retention phases yielded the maximum number of errors, this was the delay period used for all drug tests.

Drug tests

The number of errors, latency, and total time required to complete the maze did not differ among the vehicle control groups. During the information phase of the vehicle control tests, the average number of errors was 0.13 (±0.05), the latency to start was 8.2 s (±1.2), and the total time required to finish the maze was 84 s (±6.7). During the retention phase of the vehicle control tests, the average number of errors was 3.8 (±0.25), the latency to start was 6.7 s (±1.2), and the total time required to finish the maze was 135 s (±8). During the information phases of the various drug tests, there were no significant differences between dose groups on the average number of errors committed, latency to start or time required to complete this phase.

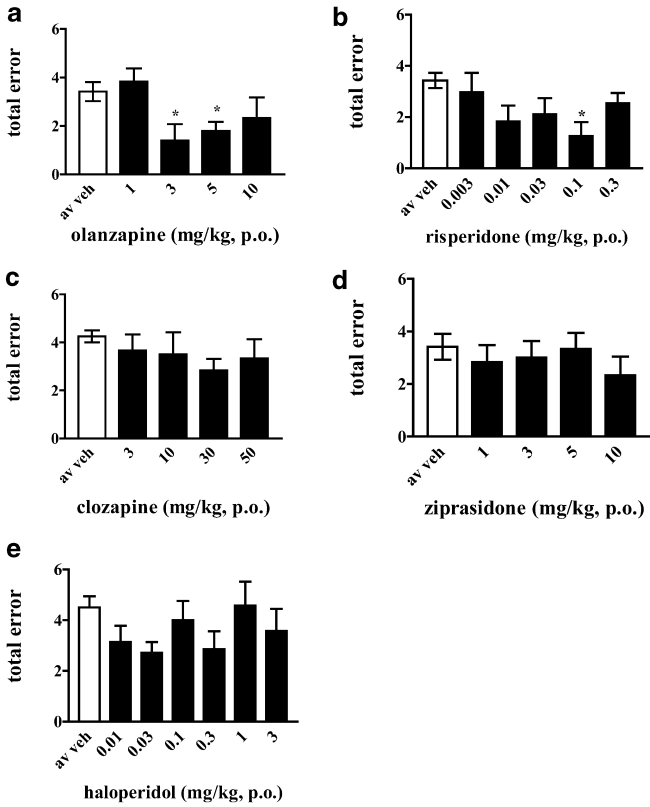


Fig. 2a-e Average number of errors that occurred during the retention phase after the oral administration of various doses of antipsychotic. Error bars indicate the SEM. * Significantly different than the average vehicle control value. **a** Olanzapine, $n=6$; **b** risperidone, $n=7$; **c** clozapine, $n=6$; **d** ziprasidone, $n=6$; **e** haloperidol, $n=7$

Olanzapine

As shown in Fig. 2a, oral administration of either 3 or 5 mg/kg olanzapine, but not higher or lower doses, improved performance during the retention phase [repeated measure ANOVA $F_{(4,20)}=10.84$, $P<0.0001$; Dunnett's: $P<0.001$]. Administration of olanzapine had no effect on the latency to start, but did increase the overall time required to complete the maze [$F_{(4,20)}=2.9$, $P=0.05$] during the retention session. The effect did not appear to be dose-related and the rats retrieved all of the available reinforcements at all doses (Fig. 3a).

Risperidone

Administration of 0.1 mg/kg (PO) of risperidone (Fig. 2b) decreased the number of errors during the retention session [$F_{(5,30)}=2.46$; $P=0.05$; Dunnett's: $P<0.05$], without affecting either the latency to start or the total time required to complete the maze during the retention session (Fig. 3b).

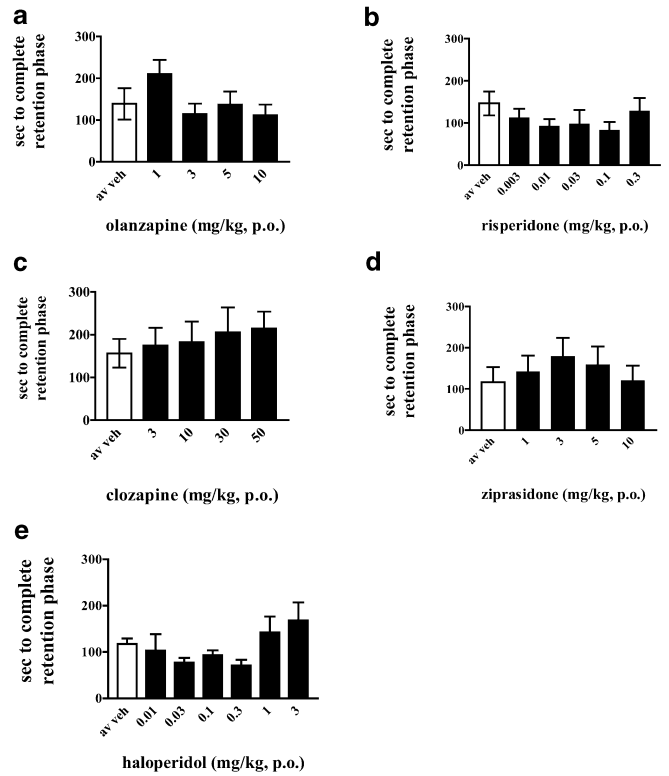


Fig. 3a-e Average length of time in seconds required to complete the retention phase after the oral administration of various doses of antipsychotic. Error bars indicate the SEM. * Significantly different than the average vehicle control value. **a** Olanzapine, $n=6$; **b** risperidone, $n=7$; **c** clozapine, $n=6$; **d** ziprasidone, $n=6$; **e** haloperidol, $n=7$

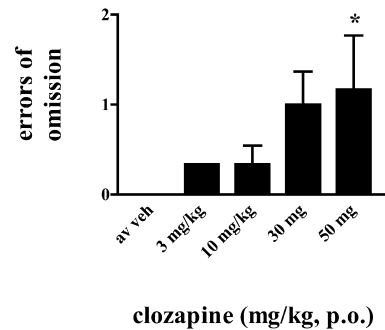


Fig. 4 Number of errors of omission during the retention session after the administration of various doses of clozapine during the same test (see Fig. 2)

Clozapine

Clozapine (Fig. 2c) failed to decrease the overall number of errors during the retention phase. However, the number of failures to enter a baited arm during the retention phase (Fig. 4) increased with increasing doses of clozapine [$F_{(4,20)}=3.01$; $P=0.04$] and was significantly different from the average vehicle control at 50 mg/kg (Dunnett's $P<0.05$). Arm choices that were made at the higher doses

of clozapine tended to be accurate. Although clozapine failed to affect the latency to start the retention session, the total time required to complete the session tended to increase with increasing doses [$F_{(4,20)}=1.9$; $P=0.15$] of clozapine (Fig. 3c).

Ziprasidone

Administration of ziprasidone (Fig. 2d) had no effect on the total number of errors during the retention session, the latency to begin, or the total time required to complete the retention session (Fig. 3d).

Haloperidol

Neither the total number of errors nor the latency to begin the retention session were affected by the administration of haloperidol (Fig. 2e). However, the time required to complete the retention session tended to increase with increasing doses of haloperidol [$F(6,36)= 2.3$; $P=0.053$]. The number of failures to retrieve rewards did not increase significantly during the retention session (Fig. 3e).

Discussion

The number of errors that occurred during the retention session increased as the delay between the information and retention phases increased. This was inferred to be due to normal forgetting during the delay period. There was no significant difference between the number of errors that occurred after relatively long delays (7 or 24 h) and the "control" situation in which the rats had no prior information as to where the food was located. Because the rats seldom returned to the same arm twice during the retention phase, there was a ceiling effect of approximately four errors in this task. This behavior reflects the natural foraging behavior of rats and is typical of a rat that has been trained in the radial arm maze.

During the course of these studies, data from a number of rats (one or two per drug) were eliminated because the rats failed to make at least two errors during both vehicle control sessions. It has been our experience that if rats are continuously tested at any one given delay between the information and retention phases, some will learn to do the task without error, even in the absence of drug. To prevent this tendency from biasing the results, each rat's performance under drug was always compared to its own baseline, obtained both before and after the period of drug administration.

The number of retention phase errors was significantly reduced after the administration of either olanzapine (3 or 5 mg/kg) or risperidone (0.1 mg/kg). Administration of clozapine, ziprasidone and haloperidol did not significantly decrease the number of errors. However, the results obtained with clozapine were somewhat ambiguous

because, at higher doses (30 mg/kg and above), three of the six rats failed to complete the maze, i.e. they were behaviorally impaired. No significant differences in performance were recorded during the information phases of any of the drug tests. Therefore, drug-enhancing effects could not have been due to differences in how well the information had been acquired during the information phase. An interpretation of the results in terms of effects on attention, motivation, sensory perception, or other functions important to task acquisition was also ruled out because the drugs were never administered until after the information phase of the test had been completed. The relatively long delay interval between drug administration immediately after the information phase and testing during the retention phases suggests that the drug would have been unlikely to have selectively affected retrieval processes. Therefore, the reduction in the number of retention phase errors after the administration of olanzapine and risperidone was probably due to an effect on consolidation processes necessary for maintaining the memory of where food had been obtained some hours earlier. However, although the half-life of these drugs was 7 h or less (Prakash 1997; Aravagiri et al. 1999; Aravagiri and Marder 2002; except clozapine: Baldessarini et al. 1993), a reduced amount of drug would still have been on board during the retention session, making it possible that these compounds could have had additional effects on retrieval processes. This may have been reflected in the dose-related increased length of time required for the rats to complete the retention session after the administration of clozapine and haloperidol. Administration of these compounds immediately before the information or retention phases would yield additional information regarding their effects on the acquisition and retrieval phases of memory.

Neither ziprasidone nor risperidone affected the time required to complete the maze or the number of food reinforcements received. However, the time required to complete the retention phase increased in a dose-related manner after the administration of clozapine and haloperidol, and in a non-dose related manner after olanzapine. In the cases of olanzapine and haloperidol, the rat was able to retrieve all of the available food reinforcements, indicating that performance was not severely disrupted. However, at the highest dose of clozapine, there was a significant increase in the number of failures to enter a baited alley indicating that the rats' behavior was disrupted by the higher doses of clozapine. Because greater doses of clozapine are required in both animal models (Moore 1999) and the clinic to achieve efficacy, clozapine exhibits relatively more anticholinergic activity than olanzapine (Chengappa et al. 2000). Drugs with strong anticholinergic properties have memory impairing effects (Bartus 2000). Although clozapine has high affinity for many of the same receptors as olanzapine (Bymaster et al. 1996), the relatively greater anticholinergic activity of high doses of clozapine, may have precluded the exhibition of memory enhancement effects from other mechanisms such as the 5-HT₆ and 5-HT_{2A}.

Relatively more activity at the histamine H₁ and the α -adrenergic receptors, as well as the longer half-life of clozapine (Aravagiri et al. 1999) might also contribute to behavioral disruption, possibly by increasing sedation that was still evident during the retention session.

Despite the fact that clinical studies have found improvement in some tests of perceptual/motor processing, attention/reaction time, executive function, and verbal learning and memory after short term treatments with clozapine, risperidone, and olanzapine (Meltzer and McGurk 1999; Purdon 1999), the pre-clinical data is inconsistent with respect to the effects of antipsychotics on learning and memory. For instance, Skarsfeldt (1996) reported that most antipsychotics, including the ones used in the present study, impaired spatial learning in the Morris water maze. Working memory tested in a delayed non-match to position task (Arnt and Skarsfeldt 1998) was also impaired. Haloperidol selectively disrupted working memory after long term administration (Levin and Johansson 1988) and significantly impaired spatial learning in Morris water maze at doses that did not affect ability to escape to visible platform (Ploeger et al. 1992). In contrast to the above results, however, Moore et al. (1997) reported that olanzapine, unlike scopolamine, had little effect on the accuracy of performance in a water maze. In general agreement with our results, risperidone improved performance in a complex maze task that assessed working memory (Nowakowska et al. 1999). Beatty and Rush (1983) found that haloperidol did not affect performance if injected immediately after the first four choices when a 5-h delay was imposed before the fifth to eighth choices in a radial arm maze. A number of important procedural differences such as the type of task, its motivation and type of memory studied, baseline performance and the time of drug administration relative to training and testing, could account for some of these discrepancies.

The effective doses of olanzapine and risperidone in the delayed radial arm maze task were similar to the doses required for efficacy in behavioral tests that are commonly used to predict antipsychotic activity (Grant and Fitton 1994; Bakshi and Geyer 1995; Moore 1999). This suggests that the beneficial cognitive effects will be obtained within the same dose range as required for antipsychotic activity and may be predicted by use of the present paradigm.

The atypical antipsychotics have a broad receptor binding profile and complex pharmacology (Bymaster et al. 1996; Schmidt et al. 2001). In order to demonstrate an effect on the consolidation process, the experimental paradigm (i.e. drug orally administered after the information session) required that the drug be readily absorbed after oral dosing. Each of the drugs tested has been reported to be rapidly absorbed after oral administration in the rat with the C_{max} occurring within 1 h (Baldessarini et al 1993; Prakash 1997; Aravagiri et al 1999; Aravagiri and Marder 2002) and detectable levels found at earlier time points. Thus the differences in error obtained during the retention phase of the present experiment were

unlikely to be due solely to pharmacokinetic differences between the drugs. Although the atypical antipsychotics share the property of having a higher affinity for the 5HT_{2A} receptor than the dopamine D₂ receptor, there are other characteristics, such as affinity for the 5HT_{1A}, 5HT₆ and 5HT₇ receptors, that they do not have in common. Given the differences between these compounds, it is likely that the atypical antipsychotics influence cognition through diverse mechanisms. Olanzapine has a number of properties that could contribute to its ability to improve cognition. For instance, olanzapine induced a robust increase in acetylcholine release in the hippocampus (Shirazi-Southall et al. 2002) as well as increased extracellular acetylcholine concentrations in the rat medial prefrontal cortex (Ichikawa et al 2002). Olanzapine also caused a dose-related increase in the extracellular concentration of dopamine in the rat prefrontal cortex (Xi-Ming et al. 1998) that may contribute to improved cognitive functioning. Olanzapine's high affinity, antagonist activity at the 5HT₆ receptor (Bymaster et al. 2001) may also be important in its ability to improve memory. Pre-clinical evidence suggests that 5HT₆ antagonists may improve cognitive function (Rogers et al. 1999), possibly by selectively enhancing excitatory neurotransmission (Dawson et al. 2001). Green (et al. 1997), suggested that risperidone might improve verbal working memory in schizophrenic patients through antagonist activity at the 5HT_{2A} receptor.

Because the cognitive impairments evident in many schizophrenics appear to be related to the severity of their negative symptoms and the patient's ability to function in society, cognitive deficits may predict the long-term outcome of schizophrenia (Breier et al. 1991). Drugs that alleviate cognitive impairments in addition to other psychotic symptoms may have an important influence on treatment outcome and the course of the illness. The data presented here suggest that olanzapine and risperidone have important cognitive enhancing properties during memory consolidation that are not present with other atypical antipsychotics, such as ziprasidone, or with typical neuroleptics, such as haloperidol. The ability to alleviate the cognitive impairments of schizophrenia will be important in the development of new drugs to treat schizophrenia. The delayed non-match to sample test in the radial arm maze provides an important pre-clinical test to study such cognitive effects.

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