Introduction

Cognitive functions are impaired in schizophrenia. Typical antipsychotic drugs usually fail to improve, and often impair, cognition. Newer, atypical medications produce stronger antago-

nism of serotonin receptors and improve aspects of cognition in some studies. Clozapine in particular has been shown to be beneficial.

Chronic clozapine administration improved a broad range of cognitive functions in schizophre-

nia (Buchanan, Holstein, and Breier, 1994). A more recent review (Meltzer and McGurk, 1998) concluded that clozapine improves aspects of attention, verbal fluency, and executive function, but its effects on verbal, working, and spatial memory are mixed. However, clozapine did improve working memory updating in schiz-

ophrenics as measured by the P300 ERP (Galletly, Clark, and McFarlane, 2005).

Clozapine’s effects on working memory in rats have been mixed. Chronic administration im-

paired acquisition in the radial-arm maze (Rosengarten and Quartermain, 2002). Acute administra-

tion had no effect on retention errors in a delayed non-match to position task (Gemperle et al., 2003).

The present study was undertaken to further test the effects of acute clozapine administra-

tion on working memory performance in normal rats. A delayed spatial alternation task was used.

Method

Thirteen adult female Sprague-Dawley adult rats were used.

A touch-screen system presented discriminanda and record responses (Fig 1). The discriminanda were two white dots presented on the left and right sides of the screen on each trial.

The rats were first trained on the spatial alternation task without delays. They were trained to touch the left and right dots on successive trials. Training con-

tinued until each rat reached a criterion of 80% correct.

Delayed spatial alternation training began next. A ran-
dom delay of 0–15 secs occurred between trials. After performance stabilized, data collection began using an A-B-A design. The baseline phase (A1: no drug) continued for 11 days.

The rats were then matched on their baseline perform-

ance and assigned randomly to one of three dose groups (0 mg/kg, 1 mg/kg, 2 mg/kg). The 1 and 2 mg/

kg doses are similar to the doses recommended at days 10 and 25 respectively during the initial treat-

ment schedule for schizophrenia (Novartis, 2005).

During the drug phase (B), clozapine or saline was in-

jected subcutaneously 1 hour prior to testing each day. The drug phase continued for 11 days.

During the drug phase, clozapine or saline was in-

jected subcutaneously 1 hour prior to testing each day for 11 days. All other aspects were identical to the A1 phase.

After the B phase ended, a 3-day washout period was allowed and the rats were again tested in the absence of clozapine (A2).

Results and Discussion

Performance for the three groups improved signi-

ficantly across the three phases (p < .01), indicat-

ing that learning of the spatial alternation task continued during the experiment (Fig 2).

In all three phases, there were delay-dependent effects on performance. Accuracy was lower with longer delays, as expected (ps < .001; Fig 3).

During acute clozapine administration the low dose group’s accuracy was significantly lower

than the control group but only at the shortest delay intervals (0-5 secs). This difference re-

mained in the A2 phase after acute clozapine administration had ended.

No other effects of clozapine were found at any of the other delay intervals.

The results suggest that acute low-dose admin-

istration of clozapine disrupts working memory performance at short, but not long, delay inter-

vals. High-dose administration did not affect working memory performance.

This finding suggests a dose-dependent and de-

lay-dependent effect of clozapine on working memory, and may help explain the mixed findings from other studies.

References


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