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Histamine H_1 receptor involvement in prepulse inhibition and memory function: Relevance for the antipsychotic actions of clozapine

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Abstract

Histamine H_1 blockade is one of the more prominent actions of the multi-receptor acting antipsychotic clozapine. It is currently not known how much this H_1 antagonism of clozapine contributes to the therapeutic or adverse side effects of clozapine. The current studies with Sprague-Dawley rats were conducted to determine the participation of histaminergic H_1 receptor subtype in sensorimotor plasticity and memory function affected by clozapine using tests of prepulse inhibition (PPI) and radial-arm maze choice accuracy. The PPI impairment caused by the glutamate antagonist dizocilpine (MK-801) was significantly attenuated by clozapine. In the current project, we found that the selective H_1 antagonist pyrilamine also reversed the dizocilpine-induced impairment in PPI of tactile startle with an auditory prepulse. In the radial-arm maze (RAM), pyrilamine, like clozapine, impaired working memory and caused a significant dose-related slowing of response. Pyrilamine, however, decreased the number of reference memory errors. We have previously shown that nicotine effectively attenuates the clozapine-induced working memory impairment, but in the current study, nicotine did not significantly alter the effects of pyrilamine on the RAM. In summary, the therapeutic effect of clozapine in reversing PPI impairment was mimicked by the H_1 antagonist pyrilamine, while pyrilamine had a mixed effect on cognition. Pyrilamine impaired working memory but improved reference memory in rats. Thus, H_1 antagonism seems to play a role in part of the beneficial actions of antipsychotics, such as clozapine.

Keywords: Histamine; H_1; PPI; Memory; Radial-arm maze

1. Introduction

The antipsychotic drug clozapine acts on multiple receptors within the brain, including dopamine D_4, serotonin 5-HT_{2a} and 5-HT_{2c}, norepinepherine α_1 and α_2, acetylcholine muscarinic and histamine H_1 receptors (Coward, 1992). It is not currently known precisely which clozapine actions are necessary for its therapeutic effects and which underlie its adverse side effects. One potential adverse side effect of clozapine is cognitive impairment. This can be especially problematic since schizophrenia itself causes cognitive impairment, which can be exacerbated by antipsychotic drug treatment. There seems to be heterogeneity of response to clozapine. There are clinical reports that clozapine reduces the cognitive impairment associated with schizophrenia (McGurk, 1999; Meltzer and McGurk, 1999; Sharma and Mockler, 1998), but other studies have found that clozapine impairs cognitive function (Classen and Laux, 1988; Goldberg et al., 1993; Hoff et al., 1996). In addition, in laboratory studies with intact rats, clozapine impairs working memory (Addy and Levin, 2002; Addy et al., 2005; Skarsfeldt, 1996) and attention (Rezvani et al., 2006). Interestingly, clozapine has been found in our studies to significantly attenuate memory impairment caused by lesions of the connections of the hippocampus carried along the fimbria-fornix (Addy et al., 2005) and the memory impairment caused by intrahippocampal application of the α4β2 nicotinic antagonist DHβE (Pocivavsek et al., 2006). The state of integrity of neural systems involved with cognitive function seems to play an important role on clozapine effects on cognitive performance. The roles of the multifaceted actions of clozapine on cognitive function can be approached by studying the effects of drugs, which more specifically inhibit one of the receptor systems blocked by clozapine. To develop better antipsychotic drugs, it is important to understand which receptor actions of drugs like clozapine are contributing to its therapeutic and/or adverse effects. Since

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histamine H_1 blockade is one of the more prominent actions of clozapine, this study will test the potential therapeutic and adverse cognitive impairing effects of the H_1 antagonist pyrilamine.

Prepulse inhibition (PPI) of the startle response is a phenomenon of neurobehavioral plasticity in which the motor response to a startling stimulus is inhibited by a preceding warning stimulus. PPI indexes a basic neural adaptive response that is impaired in a variety of neurological and psychiatric conditions, including schizophrenia (Braff et al., 2001). PPI has been used as an effective animal model for studying schizophrenia (Geyer et al., 2001). *N*-methyl-D-aspartate (NMDA) antagonists appear to mimic some features of schizophrenia in humans (Geyer et al., 2001), and the NMDA antagonist dizocilpine (formerly MK-801) robustly disrupts PPI in rats (Keith et al., 1991; Levin et al., 2007, 2005; Mansbach and Geyer, 1989). Some antipsychotics, such as clozapine, have been shown to block the dizocilpine-induced PPI impairments in rats (Bakshi et al., 1994; Bortolato et al., 2005; Bubenikova et al., 2005; Caceda et al., 2005; Martin et al., 2003). Thus, we tested the potential therapeutic effects of pyrilamine in attenuating this dizocilpine-induced PPI impairment in rats.

The effect of H_1 histamine blockade on cognition was tested in rats using the 16-arm radial-arm maze (RAM). In previous studies, clozapine has been shown to impair working memory on the RAM in intact rats (Addy and Levin, 2002; Addy et al., 2005; Levin and Christopher, 2006), and acute nicotine reversed this clozapine-induced working memory deficit (Addy and Levin, 2002). In an effort to determine which of clozapine's many neurotransmitter receptor effects are critical for its neurobehavioral actions and interactions with nicotine, we are conducting a series of studies of drugs, which act more specifically on subsets of receptors blocked by clozapine. In the current study, nicotine was given in combination with pyrilamine to determine if it would reverse any cognitive deficits induced by the H_1 antagonist. Both working and reference memory were assessed. The RAM results with pyrilamine will help determine whether H_1 receptor blockade is involved in the cognitive impairing side effects of antipsychotics such as clozapine, and the combined administration with nicotine will indicate whether or not it can reverse any cognitive impairing effects that may be observed on the RAM.

2. Methods

2.1. Animals

Twelve adult female Sprague-Dawley rats weighing 200–225 g were used for each of the two studies. Rats were on a reverse dark:light cycle with lights off at 0700 h. All rats had ad lib access to water. The rats in the PPI study also had ad lib access to food while those in the radial-arm maze study were fed daily after testing to keep them at a lean healthy weight.

2.2. Prepulse inhibition equipment

Tactile startle reflex amplitude was measured and prepulse inhibition calculated with the Med Associates Startle Reflex System (St. Albans, VT, USA). The equipment included response platforms that were placed in sound attenuating chambers. Each platform was calibrated with a spinner type calibrator (Med Associates Startle Calibrator). Prepulse tones were generated by a speaker within the chamber midway on the long axis of the platform, and the sound intensity of the speaker in each chamber was calibrated (Digital Sound Level Meter, Extech Instruments). Plexiglas cylinders large enough to allow animals to turn around (7.5 cm diameter), were mounted on the platforms, and contained an opening in the top of the tube to allow for the delivery of the 4-PSI air puff to the rat's back used to elicit the startle response. The background noise was a constant 65 db white noise.

2.3. Prepulse inhibition testing procedure

The test session was conducted in 3 blocks. After the rats were placed in the chambers, there was a 5-min acclimation period before testing began. Block 1 consisted of 6 startle only trials with a 110 dB white noise stimulus. Block 2 had a total of 48 trials: 12 startle only trials and 36 prepulse plus startle trials. Within the prepulse trials there were 3 prepulse levels: 68, 71 and 77 dB pure tone. The trials were presented in a random order with the inter-trial duration ranging from 10 to 20 s. Block 3 had an additional 5 trials of startle only. Each stimulus had a 2 ms rise/fall time. The null period was 100 ms and the prepulse/startle delay was 100 ms onset to onset. The entire test period lasted approximately 34 min.

Data from previous experiments using a startle only design revealed that the initial trials in a session could be variable. The amplitude in the first and second trials was quite low and in subsequent trials increased and reached a plateau within 6 trials. Thus, the data from Block 1 with 6 trials of startle only were not included in the analyses.

2.4. Prepulse inhibition drugs

The drugs used in the PPI test were given in a repeated measures, counterbalanced design with at least 2 days between sessions. Combinations of pyrilamine (0, 10, 20 and 40 mg/kg) and dizocilpine (0 and 0.5 mg/kg) were given via a single subcutaneous injection 10 min prior to PPI testing.

2.5. Radial-arm maze

The 16-arm RAM was made of wood and painted black. It was elevated 30 cm from the floor and had a central platform 50 cm in diameter with 16 arms (each 10×60 cm) projecting radially. Food cups were 2 cm from the distal end of the arms and were baited with Froot Loops halves (Kellogg Co., Battle Creek, MI). Testing was conducted in a quiet room with multiple extra-maze visual cues that remained in the same locations relative to the maze. Rats tested on the 16-arm RAM were food restricted to approximately 15 g/day. These rats were given 3 brief handling sessions prior to RAM training. RAM shaping began with 4 sessions to familiarize them with the food reinforcements. During these shaping sessions, individual rats

were placed in an opaque cylinder in the middle of the maze with 12 Froot Loop halves. RAM training was then carried out 3 days/week for a total of 18 sessions per rat. Only 12 of the 16 arms were baited to examine both working and reference memory errors. For each rat, the same 12 arms were baited at the beginning of each session, leaving the same four arms always unbaited. The pattern of baited and unbaited arms differed among rats with the stipulation that there were no more than 2 consecutively unbaited arms. Each session began by placing the rat in an opaque cylinder in the middle of the maze for 10 s to allow for orientation and to avoid bias as to which arm would be entered first. After the cylinder was removed, the rat was allowed to roam freely about the maze for 10 min or until all 12 baited arms had been entered. Arm choice was recorded if all four paws crossed the threshold of the arm. The arms were not rebaited, so repeated entries into a baited arm were not rewarded and were counted as working memory errors. All entries into arms that were never baited were recorded as reference memory errors. The response latency (average time per entry) was calculated by dividing the total time of the session by the number of arms entered.

2.6. Drug challenges in the radial-arm maze

The drug challenges began after the 18 sessions of RAM training when rats had reached asymptotic performance. Rats were given a single subcutaneous injection of pyrilamine and/or nicotine 20 min prior to testing. Doses of pyrilamine (0, 10, 20, and 40 mg/kg) and nicotine (0, 0.2, and 0.4 mg/kg) were dissolved in isotonic saline vehicle with dose volumes of 1 ml/kg. The 12 different doses were given in a counterbalanced order following a Latin square. At least 2 days elapsed between drug testing sessions.

2.7. Data analysis

The PPI and RAM data were evaluated by analysis of variance (ANOVA). PPI% was analyzed with dizocilpine, pyrilamine, and PPI intensity as repeated measures. Startle alone trials with the prepulse were analyzed with dizocilpine and pyrilamine as repeated measures. The RAM errors were analyzed using error type, pyrilamine, and nicotine as repeated measures. Response latency on the RAM was analyzed using pyrilamine and nicotine as repeated measures. An alpha level of 0.05 was used as the threshold for statistical significance. Planned comparisons of controls to pyrilamine, dizocilpine, and/or nicotine were conducted to determine their treatment effects. Significant interactions were followed up with tests of the simple main effects.

3. Results

3.1. Dizocilpine-induced prepulse inhibition impairment: H_1 antagonist interactions

When the effects of pyrilamine alone on PPI% were examined, we found that pyrilamine alone did not impair PPI [$F(3,33)=1.273$, $p>0.05$]. There was a significant main effect of prepulse intensity [$F(2,22)=7.520$, $p<0.01$], with higher prepulse intensities resulting in larger PPI%. There was no significant interaction of pyrilamine and prepulse intensity [$F(6,66)=1.660$, $p>0.05$] (Fig. 1). For startle alone trials, the main effect of pyrilamine was not significant [$F(1,11)<1$, $p>0.05$]. Mean amplitudes (±SEM) on startle alone trials were 381.34±72.13, 388.79±81.93, 385.20±81.56, and 414.01±78.32, for 0, 10, 20, and 40 mg/kg pyrilamine, respectively.

Dizocilpine caused a significant impairment in PPI% (Fig. 2). The main effect of dizocilpine was highly significant [$F(1,11)=41.89$, $p<0.0001$]. Dizocilpine alone caused a significant ($p<0.0001$) PPI deficit (PPI% 26.16±3.37) compared with performance after saline control injections (PPI% 53.58±2.29). The main effect of pyrilamine was also significant [$F(3,33)=3.63$, $p<0.025$] with an inverted U-shaped dose effect function with the low and middle doses increasing PPI and the highest dose approaching control-level performance. Since the dizocilpine×pyrilamine interaction was significant [$F(3,33)=8.42$, $p<0.0003$], follow-up comparisons were made at the drug interaction level. Further, the three-way interaction of dizocilpine, pyrilamine and prepulse intensity was not significant [$F(6,66)<1$, $p>0.05$], so comparisons could be made collapsing across prepulse intensity. Interestingly, the low and middle pyrilamine doses significantly ($p<0.0001$) attenuated dizocilpine-induced PPI impairment (Fig. 2). The highest pyrilamine dose was not quite significant in this regard ($p<0.06$) (Fig. 2).

The main effect of prepulse intensity was significant [$F(2,22)=46.77$, $p<0.0001$]. Each of the progressively greater prepulse intensities caused a significantly ($p<0.005$) greater inhibition in tactile startle response. There was no significant interaction of prepulse intensity with pyrilamine [$F(6,66)=1.394$, $p>0.05$]. There was a significant interaction of prepulse intensity with dizocilpine [$F(2,22)=6.11$, $p<0.01$]. However, follow-up tests of the simple main effects showed that

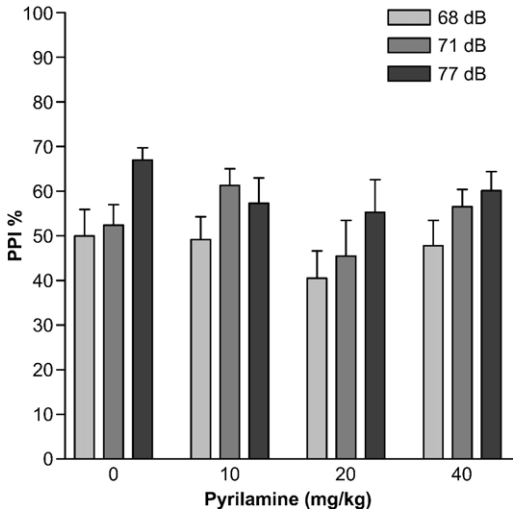

Fig. 1. The interaction of pyrilamine and prepulse intensity was not significant nor was the main effect of pyrilamine, when PPI% was analyzed for the pyrilamine data. Increasing prepulse intensity significantly increased %PPI.

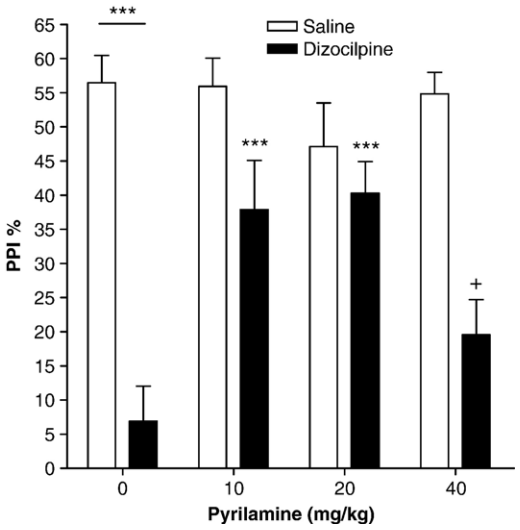

Fig. 2. Dizocilpine significantly decreased %PPI compared to saline alone (denoted by the bar). There was also a significant dizocilpine × pyrilamine interaction for %PPI. Pyrilamine at 10 mg/kg and 20 mg/kg significantly attenuated the dizocilpine-induced PPI impairment, while the 40 mg/kg dose of pyrilamine did not quite reach significance. Data are presented collapsed across prepulse intensity because the three-way interaction of dizocilpine, pyrilamine and prepulse intensity was not significant. *** Denotes a difference from dizocilpine alone at $p<0.001$, + denotes a difference from dizocilpine alone at $p<0.1$.

dizocilpine caused a significant PPI impairment at all levels of prepulse intensity.

Dizocilpine caused a significant increase in startle alone [$F(1,11)=14.23$, $p<0.005$]. Pyrilamine did not quite cause a significant effect ($p<0.06$). The higher doses of pyrilamine tended to increase startle alone. The interaction of dizocilpine and pyrilamine was not significant.

3.2. Radial-arm maze

When the effects of pyrilamine were examined alone, there was a significant interaction of error type and pyrilamine [$F(3,33)=13.14$, $p<0.025$] (Fig. 3). Pyrilamine tended to increase working memory errors (Fig. 3). Post-hoc comparisons found that 20 mg/kg pyrilamine significantly increased the number of working memory errors compared to saline injection ($p<0.05$), and 40 mg/kg pyrilamine caused a near significant increase in working memory errors over saline ($p<0.08$). In contrast, pyrilamine dose-dependently decreased reference memory errors (Fig. 3). Post-hoc comparisons revealed that 40 mg/kg of pyrilamine caused a near significant ($p<0.06$) decrease in reference memory errors compared to saline injections (Fig. 3). The main effect of error type was also significant [$F(1,11)=11.44$, $p<0.01$], indicating that all rats made on average more working memory (5.11±0.49 errors) than reference memory errors (3.08±0.17 errors). The main effect of pyrilamine was also significant for response latency [$F(3,33)=12.90$, $p<0.001$]. Post-hoc comparisons revealed that 20 mg/kg and 40 mg/kg of pyrilamine significantly increased response latency over saline injections ($p<0.01$ and $p<0.001$, respectively). Mean (±SEM) response latency for controls was 13.38±1.13 s/arm entry, while mean response latencies for 10, 20, and 40 mg/kg pyrilamine were 12.97±1.09, 25.47±3.65, and 28.79±3.55 s/arm entry, respectively.

RAM error analyses including nicotine and pyrilamine revealed only a significant main effect of error type [$F(1,11)=11.42$, $p<0.01$]. Again, all rats made on average more working memory (5.49±0.38 errors) than reference memory errors (3.20±0.14 errors). All other interactions and main effects were non-significant. Nicotine did not significantly attenuate or facilitate the effects of pyrilamine on RAM errors. Nicotine did not alter response latency [$F(2,22)<1$, $p=0.514$]. Pyrilamine was found again to significantly increase the response latency [$F(3,33)=30.42$, $p<0.001$], and post-hoc comparisons found that 20 mg/kg and 40 mg/kg of pyrilamine significantly increased the response latency over saline ($p<0.001$).

4. Discussion

4.1. Pyrilamine effects on prepulse inhibition

As seen previously (Keith et al., 1991; Levin et al., 2007, 2005; Mansbach and Geyer, 1989), dizocilpine significantly impaired tactile PPI. Dizocilpine also increased startle on trials without a prepulse, which is an effect that has been observed previously (Bubenikova et al., 2005; Levin et al., 2005). Like clozapine (Bakshi et al., 1994; Bortolato et al., 2005; Bubenikova et al., 2005; Caceda et al., 2005; Martin et al., 2003), pyrilamine significantly attenuated the dizocilpine-induced tactile PPI impairment. The attenuation of the dizocilpine-induced PPI impairment did not seem to be due to a reversal of the effects of dizocilpine on startle alone. Pyrilamine also tended to increase startle on the trials without a prepulse. Previous studies in our lab did not find a change in startle amplitude with clozapine treatment with acoustic startle

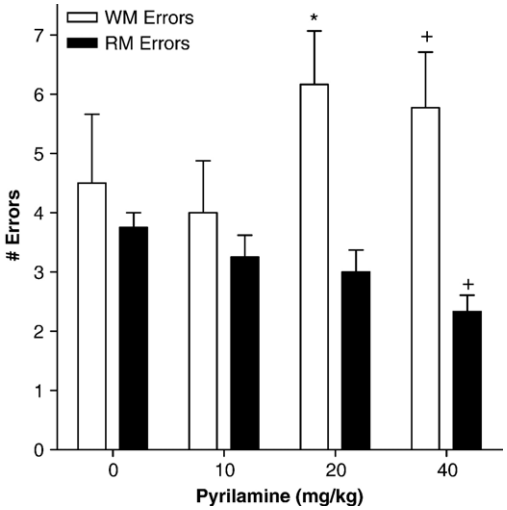

Fig. 3. There was a significant interaction of error type and pyrilamine. Pyrilamine tended to increase working memory (WM) errors, while it dose-dependently decreased reference memory (RM) errors, * denotes a difference from saline controls at $p<0.05$, + denotes a difference from saline controls at $p<0.1$.

(Levin et al., 2005) but did see a decrease in startle response with tactile startle as was used in the current study (Levin et al., 2007). Some studies report a reduction in startle magnitude with clozapine (Bortolato et al., 2005; Bubenikova et al., 2005; Conti et al., 2005; Schwabe et al., 2005; Swerdlow et al., 2006), while others report no significant changes (Caceda et al., 2005; Tenn et al., 2005). However, the effects of antipsychotics on PPI are believed to be independent of effects on startle amplitude (Johansson et al., 1995).

The role of the histamine receptor in PPI has not been widely studied. Previous studies have shown that the H_3 receptor antagonists thioperamide, ciproxifan, and ABT-239 improve the intrinsic PPI deficits observed in DBA/2 mice (Browman et al., 2004; Fox et al., 2005). A recent study provides support for the role of the H_1 receptor in PPI using an H_1 receptor gene knockout mouse model (Dai et al., 2005). They found that social isolation significantly impaired PPI of the startle response in the wild-type mice but not in the H_1 receptor knockout mice (Dai et al., 2005). Further, they report that repeated treatment with pyrilamine significantly improved the PPI impairment caused by social isolation in wild-type mice (Dai et al., 2005).

4.2. Pyrilamine and nicotine interactions on working memory on the radial-arm maze

Similar to clozapine (Addy and Levin, 2002; Addy et al., 2005; Levin and Christopher, 2006), pyrilamine impaired working memory in intact rats, and previous RAM studies with pyrilamine in rats have found working memory impairments (Chen et al., 2001; Nishiga et al., 2002a,b; Taga et al., 2001). In addition, intrahippocampal administration of pyrilamine impaired memory on the three-panel runway task (Nakazato et al., 2000). Interestingly, a PET study found that at least 70% of the H_1 receptors had to be blocked to impair cognitive performance in human subjects (Yanai et al., 1999).

Generally, histamine release from histaminergic neurons facilitates short-term memory (Philippu and Prast, 2001; Prast et al., 1996). Thus, histamine, histidine, and H_3 receptor antagonists/inverse agonists all cause histamine release in the brain facilitating short-term memory. For example, H_3 receptor antagonists, thioperamide and ciproxifan, significantly attenuated scopolamine-induced water maze deficits, and ciproxifan showed a modest attenuation in the Barnes maze (Komater et al., 2005). However, there are some exceptions to the rule. We recently found that thioperamide increased the number of errors on the repeated acquisitions version of the 8-arm RAM in which a different set of 3 arms are baited each day (Kholdebarin et al., 2005).

Conversely, the inhibition of histamine synthesis deteriorates memory processes (Philippu and Prast, 2001). H_3 receptors agonists decrease the neuronal release of histamine and impair cognitive performance in rats measured by object recognition and a passive avoidance task (Philippu and Prast, 2001).

Acute nicotine reverses the working memory deficit induced by clozapine (Addy and Levin, 2002), but in this study, acute nicotine did not reverse the working memory deficit induced by pyrilamine. Nicotine has been shown to improve working memory in rats (Levin et al., 2006), but in this study, acute nicotine in a repeated measures design did not improve working memory. Previous studies in our lab have also found variation in the nicotinic effect on working memory when using the repeated measures design (Addy and Levin, 2002), and this may be due to some carryover effect of the drug treatments.

4.3. Pyrilamine effects on reference memory

Pyrilamine caused a marginal improvement in reference memory on the RAM. Pyrilamine did slow response latency, but it did not decrease the number of arm entries made. Thus, the decrease in reference memory errors observed with pyrilamine was not due to decreased opportunities to make reference memory errors. Studies in another laboratory have reported increased reference memory errors in rats given pyrilamine (Nishiga et al., 2002a,b; Taga et al., 2001). Those studies evaluated reference memory using an 8-arm RAM with only 4 of the arms baited. In addition, they trained their rats until they reached a criterion of at most 1 error per trial for five successive trials, which according to one paper took 36 days of training (Nishiga et al., 2002b). In comparison, our rats received only 18 training sessions on the more difficult 16-arm RAM prior to the pyrilamine sessions. Thus, the difference between studies may be explained by the differences in the number of arms on the RAM or in the amount of prior training. In fact, comparing baseline performance following saline injections, their rats on average made less than 1 reference memory error, while our rats were making close to 4 reference memory errors on average.

In studies of avoidance learning, intracereberoventricular injections of pyrilamine improved memory retention in rats in passive avoidance (Eidi et al., 2003), but in other studies, systemic pyrilamine impaired learning in shuttle box and step-through active avoidance tests (Kamei et al., 1990; Tasaka et al., 1986). Thus, the effects of pyrilamine on long-term memory are equivocal. Astemizole is an H_1 receptor antagonist that does not enter the brain to any appreciable degree (Handley et al., 1998), and systemic administration in mice did not impair long-term memory in a passive avoidance test (Swiader et al., 2003). Thus, the effects of pyrilamine on long-term memory are likely mediated by central nervous system H_1 receptor antagonism.

Histamine appears to differentially affect working and reference memory. A recent RAM study found that histamine ameliorated the dizocilpine-induced impairments on working and reference memory. However, H_1 antagonist pyrilamine or H_2 antagonist cimetidine injected into the ventral hippocampus abolished these ameliorating effects of histamine for only reference and not working memory (Xu et al., 2005). Thus, H_1 and H_2 receptors in the ventral hippocampus are involved in histamine's effects on reference memory but not working memory (Xu et al., 2005). Histamine's effects on working memory appear to be mediated by other neuronal pathways within the ventral hippocampus (Xu et al., 2005).

It is currently unknown if clozapine would likewise improve reference memory on the RAM. Previous studies were not conducted on the larger 16-arm maze where reference and working memory can be differentiated. Nicotine did not

significantly alter the effects of pyrilamine on reference memory.

5. Conclusions

Histamine H_1 blockade appears to be a beneficial action of antipsychotics, such as clozapine, based on its therapeutics effects in the PPI test and improved reference memory on the RAM test. Like clozapine, H_1 histamine blockade did impair working memory function. Future studies will examine other individual receptor actions of clozapine in order to optimize the function of antipsychotics and result in fewer side effects.

Acknowledgements

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