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European Journal of Pharmacology 486 (2004) 175–182
www.elsevier.com/locate/ejphar

Nicotine–antipsychotic drug interactions and attentional performance in female rats

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Received 15 September 2003; accepted 10 December 2003

Abstract

Schizophrenia is marked by pronounced cognitive impairments in addition to the hallmark psychotic symptoms like hallucinations. Antipsychotic drugs can effectively reduce these hallucinations; however, the drugs have not resolved the cognitive impairment. Interestingly, nicotine, a drug commonly self-administered by people with schizophrenia, has been shown to significantly improve cognitive function of people with schizophrenia. The current study was conducted to determine the effect of typical (haloperidol) and atypical (clozapine and risperidone) antipsychotic drug treatment on sustained attention in rats performing a visual signal detection task. In addition, the interaction of haloperidol with chronic nicotine administration was assessed. Female Sprague–Dawley rats were injected subcutaneously with clozapine (0, 0.6, 1.25 and 2.5 mg/kg), risperidone (0, 0.025, 0.05 and 0.1 mg/kg) or haloperidol (0, 0.01, 0.02 and 0.04 mg/kg). In the second part of the study, the interaction of acute haloperidol (0, 0.005, 0.01 and 0.02 mg/kg) and chronic nicotine (5 mg/kg/day, for 4 weeks via osmotic minipump) was characterized. Clozapine, risperidone and haloperidol all caused dose-related impairments in percent hit performance. There was a significant linear dose-related impairment in percent hit caused by risperidone. All the doses of clozapine caused a significant impairment in percent hit at the higher luminance intensities in the visual signal detection task. The 0.01 and 0.02 mg/kg haloperidol doses caused significant decreases in percent hit. The 0.04 mg/kg haloperidol dose impaired performance of the task to the point that reliable choice accuracy measurements could not be made. Chronic nicotine infusion significantly diminished the impairing effects of haloperidol on performance during weeks 1–2. In summary, both typical and atypical antipsychotic drugs significantly impaired sustained attention in rats. Haloperidol was more detrimental than clozapine and risperidone. Chronic nicotine diminished the adverse effects of haloperidol on performance. This study establishes a paradigm to reliably determine the attentional impairment caused by antipsychotic drugs.

Keywords: Attention; Haloperidol; Clozapine; Risperidone; Cognition; Signal detection task

1. Introduction

Attentional function is substantially impaired in most patients with schizophrenia (Benedict et al., 1994; Nuechterlein, 1991). Typical antipsychotic drugs, such as haloperidol, have not been found to help reverse this attentional impairment. In fact, haloperidol has been found to potentiate the attentional impairment of schizophrenia (Levin et al., 1996a). Newer atypical antipsychotic drugs, such as clozapine and risperidone, may not impair attentional function as much as haloperidol. Indeed, it has been found that clozapine improves attention and verbal fluency and that risperidone has positive effects on working memory and attention in schizophrenia (Meltzer and McGurk, 1999).

The effects of nicotine are important because nicotine has been shown to significantly improve attention in humans (Lawrence and Sahakian, 1995; Levin et al., 1996a,b, 1998, 2001; Peeke and Peeke, 1984; Sahakian et al., 1989; Warburton et al., 1992; White and Levin, 1999) and rodents (Grilly et al., 2000; Mirza and Bright, 2001; Mirza and Stolerman, 1998; Muir et al., 1995; Rezvani et al., 2002; Rezvani and Levin, 2003a,b; Stolerman et al., 2000). In fact, self-medication with nicotine may underlie the high smoking rates by people with schizophrenia (Lohr and Flynn, 1992). Nicotine delivered via transdermal patch has been shown to significantly improve attentional performance in patients with schizophrenia regardless of the haloperidol dose (Levin et al., 1996a). Nicotine has also been shown to significantly improve attentional performance in other clin-

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doi:10.1016/j.ejphar.2003.12.021

ical groups including adults with attention deficit hyperactivity disorder, patients with Alzheimer's disease and people with age-associated memory impairment, as well as normal young adults (Levin et al., 1996b, 1998, 2001; White and Levin, 1999, 2004-in press).

In previous studies, we have found that nicotine can significantly improve attentional performance of rats in an operant visual signal detection task (Rezvani et al., 2002; Rezvani and Levin, 2003a,b). Operant visual signal detection techniques have been used to study attention in rats (Bushnell, 1998; McGaughy et al., 1999; Rezvani et al., 2001, 2002, 2003a,b; Sarter et al., 2001; Turchi et al., 1995). This task is a sensitive technique in which both sensory and attention can be simultaneously measured. Animals are required to discriminate between signals and non-signals. (Bushnell et al., 1997; Sarter et al., 2001). We have demonstrated that nicotine can partially counteract dizocilpine-induced attentional impairment in this task (Rezvani and Levin, 2003a).

Understanding the interaction between antipsychotic drugs and nicotine in attentional function may have important clinical implications. Because a large portion (85–90%) of people with schizophrenia heavily smoke tobacco products, it is important to understand the effects of the co-administration of nicotine and antipsychotic medications. Nicotine may reverse or diminish some of the cognitive deficits associated with schizophrenia because it interacts with several neurotransmitters including dopamine (Wonnacott et al., 1989). Nicotine may help to reduce the cognitive deficits associated with the blockade of dopamine transmission by antipsychotic drugs.

In the current study, the operant visual signal detection task was used to evaluate the acute effects of typical (haloperidol) and atypical (clozapine and risperidone) antipsychotics on sustained attention. In a follow up experiment, the interactions of nicotine with haloperidol were investigated. It was hypothesized that both typical and atypical antipsychotic drugs will impair attention and that chronic nicotine administration will diminish the adverse effects of haloperidol in the attention task.

2. Methods and materials

2.1. Animals

Adult (60 days old at the beginning of training) female Sprague–Dawley rats ($N=35$) (Taconic Farms, Germantown, NY, USA) were used. Rats were housed in groups of three in plastic cages with wood shavings in an animal colony room with 12L/12D light schedule (light on at 7:00 p.m.). Animals remained under the reversed-light cycle for 3 months before the experiments began. Room temperature was controlled at 21 ± 1 °C and relative humidity at $50 \pm 10\%$. Rats had free access to water in their home cage and were fed daily after testing such that their weights were kept at 85% of their ad lib weights. Rats weighed 260 ± 3 g when the injection was initiated. All training and testing sessions were performed between 9:00 a.m. and 5:00 p.m., i.e. during the dark phase of the circadian cycle. The treatment and care of the animals was carried out under a protocol approved by the Animal Care and Use Committee of Duke University in an AAALAC-approved facility.

2.2. Experimental protocol

To characterize the effects of typical and atypical antipsychotic drugs (haloperidol, clozapine and risperidone) on attentional performance and the interaction of haloperidol and nicotine in this task, two sets of experiments were carried out. In Experiment 1, a dose-function for these antipsychotic drugs was determined. In Experiment 2, chronic nicotine interaction with haloperidol was explored.

2.2.1. Experiment 1. Antipsychotic dose-effect function

Animals ($N=11$, 12, 11 for clozapine, risperidone and haloperidol, respectively) were injected subcutaneously with vehicle or one of the doses of clozapine (0.6, 1.2 and 2.5 mg/kg), risperidone (0.025, 0.05 and 0.1 mg/kg) or haloperidol (0.01, 0.02, 0.04 and 0.08 mg/kg). Ten minutes later, animals were transferred into operant boxes for testing. Rats in each group received each treatment following a counter-balanced design. The interval between injections was at least 48 h.

2.2.2. Experiment 2. Nicotine interactions with haloperidol

To determine the interaction of haloperidol with the nicotine, animals were treated chronically for 28 days with saline ($n=16$) or with 5 mg/kg/day nicotine ($n=18$) via osmotic pump (Model 2ML4, Alzet, Palo Alto, CA). The mean pumping rate for those pumps was 2.61 ± 0.15 S.D. microliters/h. Six days after surgery, the animals were injected subcutaneously with 0, 5, 10 or 20 μg/kg haloperidol during weeks 1–2, weeks 3–4 and 2 weeks after the removal of the pump. Testing began 10 min after drug injection. The time interval between injections was at least 72 h. Rats in each group received all treatments following a counter-balanced design.

2.3. Drug preparation and dosing

Haloperidol (American Pharmaceutical Partner, Los Angeles, CA, USA) was prepared by diluting a stock solution of 5 mg/ml with saline. Clozapine, risperidone and nicotine ditartrate (Sigma, St. Louis, MO, USA) were prepared in saline solution. All doses refer to the weight of the salt. Each solution was injected subcutaneously in a volume of 2 ml/kg body weight.

2.4. Chronic nicotine administration

Osmotic minipumps (Alzet, Model 2ML4) were used for the chronic nicotine administration. The pumps were

implanted subcutaneously into a pocket made by a blunt instrument in an incision between the scapulae. The incision was closed with surgical clips after the minipump was implanted. Nicotine ditartrate was delivered in a dose of 0 or 5 mg/kg/day. This dose rate was chosen to match plasma levels seen in heavy smokers (Lichtensteiger et al., 1988; Murrin et al., 1987; Trauth et al., 1999) and has been shown to increase neuronal cholinergic receptor expression in adult rats (Slotkin, 1992; Trauth et al., 1999). Behavioral testing resumed 5 days after the surgery.

2.5. Visual signal detection task

The operant chambers 29 × 25 × 29 cm (HWD) were equipped with a signal light; a house light; two retractable levers 13 cm apart and 2.5 cm above the floor of the chamber and inserted horizontally 2.5 cm into the chamber; a food cup in the center of the front panel of the chamber 2.2 cm above the floor (Coulbourn Instruments, Lehigh Valley, PA, USA), and a white noise amplifier (Med Associates, Georgia, VT, USA) mounted above the signal lever generating background white noise of about 65 dB. The signal or cue light was located above the food cup at the center of the front panel, 28 cm above the floor of the chamber. A signal consisted of 500 ms increase in the brightness of the signal light, to levels of 0.027, 0.073, 0.148, 0.269, 0.466, 0.762 and 1.22 lx above a background illumination of 1.2 lx. Signals were generated using Windows based Med Associates software running a Pentium computer processor.

The task, illustrated in Fig. 1, was conducted in daily 240-trial sessions, divided into three 80-trial blocks, each block approximately 15 min. in duration. Two-trial types, "signal" and "blank", were presented in an equal number per session, in groups of four (two signal and two blank, in random order) at each signal intensity. Each signal trial included a pre-signal interval, the signal (cue light) and a post-signal interval. The pre-signal intervals were selected randomly from 12 different values ranging from 0.3 to 24.4 s. Following the signal, a post-signal interval of 2, 3 or 4 s (selected randomly) occurred. These temporal parameters yield a trial presentation rate of 5 trials/min. Blank trials were presented identically to the signal trials, but without a cue light.

Rats were trained to perform the visual signal detection task (Bushnell, 1998; Bushnell et al., 1997; Sarter et al., 2001). A trial began with both levers retracted from the chamber. Then, at the end of the post-signal interval, both levers were inserted into the chamber simultaneously. The levers were both retracted when one was pressed or if 5 sec passed without a response. If the rat failed to press a lever, a response failure was recorded and the trial was not repeated. Every correct response (a press on the signal lever in a signal trial or a press on the blank lever in a blank trial) was followed by the illumination of the food cup and delivery of one 20-mg food pellet. After each incorrect response (i.e. a press on the signal lever in a blank trial or a press on the blank lever in a signal trial), or response failure, the rat received a 2-s period of darkness (time out). For half the rats, the left lever was defined as the signal lever and the right lever as the blank lever; the opposite assignment was made for the remaining rats (Rezvani et al., 2002; Rezvani and Levin, 2003a,b). It took about 3 months to train the animals.

2.6. Behavioral measures and statistical analysis of data

The following dependent variables were taken in each experiment: percent hit, percent correct rejection, response

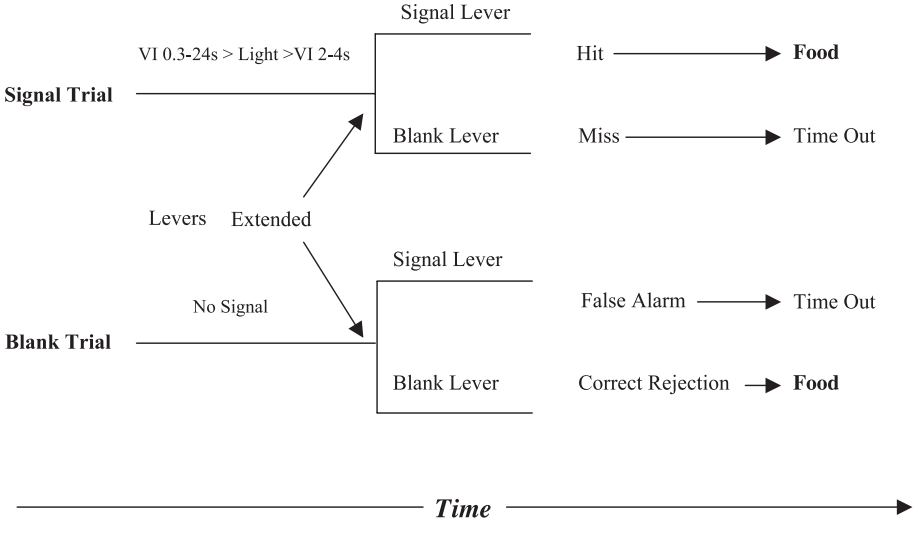

Fig. 1. Signal detection task sequence of trials. This task comprises two types of trials, signal and blank, which differ only in that during the signal trial the lever is associated with a signal light (cue) and during the blank trial the signal light is omitted. In each trial, the rat presses either of two retractable levers to report that a light signal had or had not occurred in that trial. Four possible outcomes result in each trial: hit, miss, false alarm and correct rejection. Hits and correct rejections are followed by the delivery of food (reinforcement); misses and false alarms are followed by a 2-s total darkness (time out) without delivery of food. VI stands for variable intervals for pre- and post-signal during the signal trial.

latency and response omissions. The analysis of percent hit also included light stimulus intensity as a within-subject factor. The test session was divided into 3 blocks of 80 trials and measures of response accuracy were analyzed across blocks as a repeated measure. The threshold for significance was $p < 0.05$. The Huynh-Feldt correction was used to correct for non-sphericity of variance across the repeated measures. The Superanova/Statview computer program (SAS, Cary, NC) was used for the statistical analysis. Linear and quadratic trend analyses were used to determine the monotonic and inverted-U shaped functions with increasing doses. Significant interactions were followed-up by tests of the simple main effects.

3. Results

3.1. Experiment 1. Antipsychotic dose-effect function

3.1.1. Percent hit

Compared with control vehicle, subcutaneous administration of clozapine in most instances reduced percent hit suggesting impairment in sustained attention. This effect was more pronounced ($p < 0.05$ and $p < 0.005$) at higher luminance intensities (Fig. 2). Systemic administration of risperidone significantly ($p < 0.001$) reduced percent hit (Fig. 3). The 0.1 mg/kg risperidone dose caused a significant ($p < 0.001$) decrease in percent hit, which did not vary over the different luminance intensities. Compared with control vehicle, administration of the low dose of haloperidol significantly ($p < 0.05$) caused impairment in percent hit response. With saline the rats averaged 64.7 ± 4.7% hit while with 0.01 mg/kg of haloperidol they averaged 52.6 ± 3.3% hit. There was no significant interaction of haloperidol treatment with luminance intensity. The higher doses of haloperidol (0.02 and 0.04 mg/kg) disrupted performance to the extent that percent hit could not be characterized at different intensities.

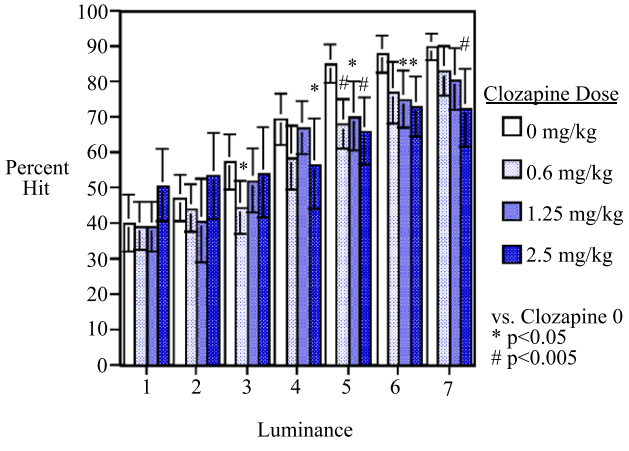

Fig. 2. Effects of different doses of clozapine on percent hit in the visual signal detection task across different luminance levels. Injections were given subcutaneously 10 min before the test (means ± S.E.M.). $N = 35$.

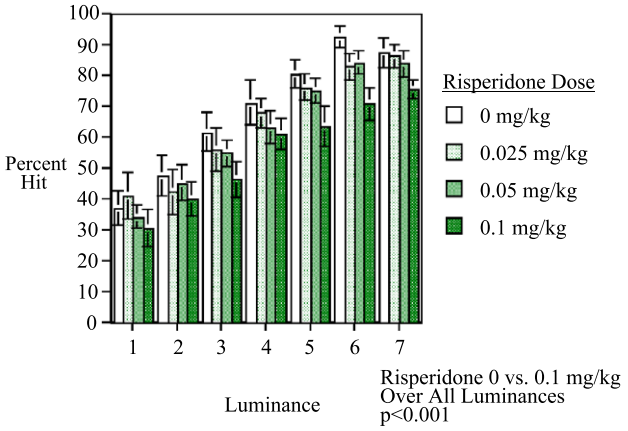

Fig. 3. Effects of different doses of risperidone on percent hit in the visual signal detection task across different luminance levels. Injections were given subcutaneously 10 min before the test (means ± S.E.M.). $N = 35$.

3.1.2. Percent correct rejection

The higher dose of clozapine dose (2.5 mg/kg) caused a significant ($p < 0.05$) decline in percent correct rejection to 61.1 ± 7.3% from 79.7 ± 3.5% with control vehicle. The lower doses of clozapine (0.6 and 1.25 mg/kg) did not exert any significant effects on percent correct rejection. No significant effect of risperidone was seen on correct rejection. The 0.01 mg/kg haloperidol dose caused a nearly significant ($p < 0.08$) decline in percent correct rejection to 78.6 ± 2.8% from 83.2 ± 2.8% with saline. The higher doses of haloperidol (0.02 and 0.04 mg/kg) disrupted performance so that percent correct rejection could not be determined.

3.1.3. Response omissions and response latency

The higher dose of clozapine (2.5 mg/kg) caused a significant ($p < 0.025$) increase in response omissions ms, 34.5 ± 11.1 vs. 4.9 ± 4.8 ms with control. The lower clozapine doses (0.6 and 1.25 mg/kg) did not cause significant changes in the response omissions rate. Both the 2.5 mg/kg (775 ± 119, $p < 0.005$) and the 1.25 mg/kg (674 ± 127 ms, $p < 0.05$) clozapine doses caused significant increases in response latency compared to control vehicle (420 ± 67 ms). Risperidone did not significantly affect the rate of response omissions, but the 0.1 mg/kg (565 ± 97 ms, $p < 0.05$) and the 0.05 mg/kg (555 ± 106 ms, $p < 0.05$) risperidone doses significantly increased response latency compared to control (449 ± 76 ms). The 0.01 mg/kg haloperidol dose caused a significant ($p < 0.025$) increase in response omissions, 22.8 ± 11.1 vs. 0.1 ± 0.1 with control, but did not significantly alter response latency. At the higher doses of haloperidol, the rats nearly ceased responding.

3.2. Experiment 2. Chronic nicotine haloperidol interactions

3.2.1. Percent hit

In weeks 1–2 of the nicotine study (Fig. 4), there was a significant nicotine × haloperidol interaction ($p < 0.005$).

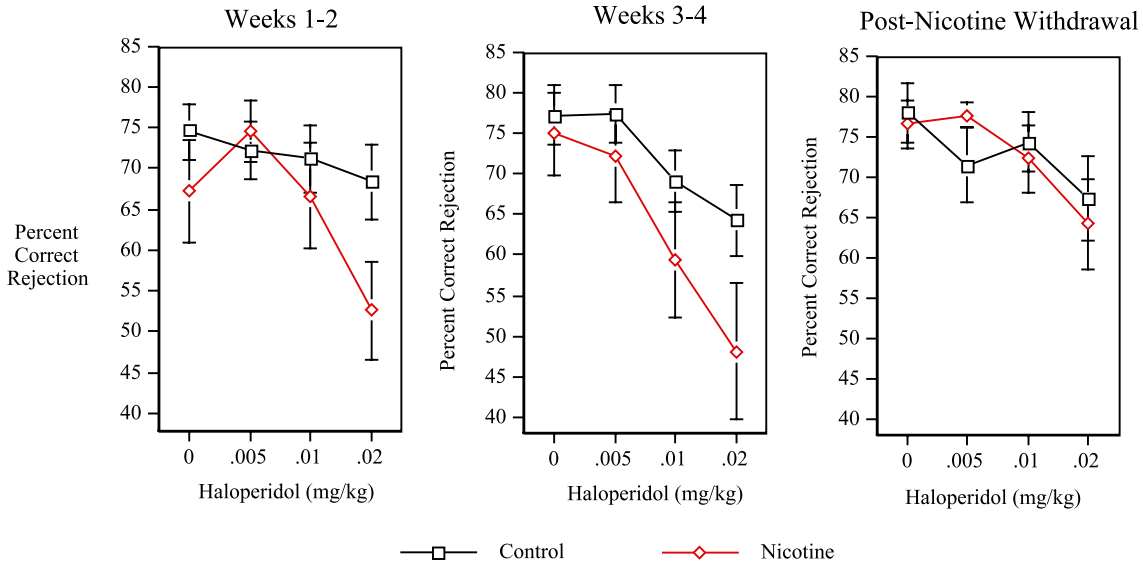

Fig. 4. Effects of different doses of haloperidol on percent hit in animals chronically treated with vehicle or 5 mg/kg/day nicotine via osmotic pumps for 28 days. Weeks 1–2 refers to the first 2 weeks of chronic treatment; weeks 3–4 refers to the last 2 weeks and post-nicotine refers to the withdrawal period when the nicotine pump was removed (means ± S.E.M.). $N = 35$.

Haloperidol caused a significant ($p < 0.0001$) linear dose-dependent decline in percent hit performance in rats not treated with nicotine. Both the 0.01 mg/kg ($p < 0.05$) and the 0.02 mg/kg ($p < 0.0001$) doses caused significant impairment in percent hit in animals which received chronic saline. In contrast, haloperidol did not cause any significant effect on nicotine-treated rats in weeks 1–2 (linear dose-effect $p = 0.77$). There was a significant nicotine-induced reduction of the linear dose effect function of haloperidol vs. controls during weeks 1–2 ($p < 0.01$). This effect of nicotine diminished during weeks 3–4 such that there was no significant differential effect of haloperidol between nicotine and placebo infused groups (Fig. 4). There was also no significant differential effect of haloperidol on percent hit during the 2 weeks after withdrawal from chronic nicotine (Fig. 4).

3.2.2. Percent correct rejection

Haloperidol caused a significant reduction in percent correct rejection ($p < 0.05$), with the higher (65.8 ± 3.5%), but not the lower haloperidol dose (73.4 ± 2.8%), causing a significant ($p < 0.05$) impairment relative to control (73.0 ± 3.1%). There was no significant effect of nicotine during weeks 1–4 of administration or withdrawal effect after cessation of treatment. The interaction of nicotine and haloperidol during weeks 1–4 and after nicotine withdrawal was not significant.

3.2.3. Response omissions and response latency

Response omissions were significantly increased by chronic nicotine treatment with main effects of nicotine during weeks 1–2 ($p < 0.005$) and 3–4 ($p < 0.001$). Without haloperidol treatment, the nicotine-treated group had 22.9 ± 7.6 omissions during weeks 1–2 and 16.4 ± 7.0 omissions during weeks 3–4, while the control groups had 1.3 ± 0.7 and 8.4 ± 5.7 omissions during the same periods. After removing the pump, there were no significant nicotine-related effects. Haloperidol administration increased the incidence of response omissions. There were significant haloperidol dose-related increases in response omissions during all three periods ($p < 0.0001$), going up from 13.5 ± 4.7, 12.9 ± 4.6 and 7.6 ± 3.2 omissions without haloperidol during weeks 1–2, weeks 3–4 and the nicotine withdrawal period, respectively, to 35.9 ± 6.2, 54.5 ± 6.0 and 39.3 ± 5.8 for the same periods with 0.02 mg/kg haloperidol. This effect of haloperidol on response omissions was not seen to significantly interact with nicotine treatment.

Haloperidol did not exert a significant effect on response latency during weeks 1–2. However, haloperidol caused a significant linear dose related increase ($p < 0.025$) in response latency during weeks 3–4 (haloperidol 0 mg/kg = 735 ± 84 ms, haloperidol 0.005 mg/kg = 759 ± 81 ms, haloperidol 0.01 mg/kg = 857 ± 97 ms, haloperidol 0.02 mg/kg = 1600 ± 116 ms). A similar significant ($p < 0.01$) linear dose effect of haloperidol was seen during the 2-week nicotine withdrawal period (haloperidol 0 mg/kg = 626 ± 55 ms, haloperidol 0.005 mg/kg = 634 ± 59 ms, haloperidol 0.01 mg/kg = 743 ± 68 ms, haloperidol 0.02 mg/kg = 891 ± 113 ms). No significant effects of nicotine or nicotine × haloperidol interactions were detected.

4. Discussion

The primary findings of these studies suggest that both typical (haloperidol) and atypical (clozapine and risperidone) antipsychotic drugs cause significant impairments of

sustained attention in female rats as measured by choice accuracy on the visual signal detection task. Although all three drugs exerted a significant impairing effect on hit response, the effect of haloperidol was more pronounced such that the high dose of haloperidol completely disrupted performance of the task. Both clozapine and haloperidol had a significant effect on correct rejection and response omission; however, risperidone did not impair either correct rejection or response omission even at a high dose of 0.1 mg/kg. These drugs have different pharmacological profiles and their differential potency in impairment of the attention task might stem from their differential actions on a different subtype of dopamine and serotonin receptors.

Dopamine, as a key neurotransmitter in the brain, plays a paramount role in cognition. Phylogenetic evidence suggests the importance of the dopaminergic system in the development of cognitive functions through evolution (Nieoullon, 2002). More specifically, sustained attention processes have been shown to be governed or regulated by dopaminergic neurons (Brockel and Fowler, 1995; Nieoullon, 2002). This has been best demonstrated by pharmacological manipulations of dopamine transmission (Brockel and Fowler, 1995) and by dopamine depletion (for review, see Nieoullon, 2002). More specifically, recently, it has been shown that impairment of attentional processes is positively correlated with elevated dopamine D_2 receptors in the frontal lobe of schizophrenic patients (Oades et al., 2000).

The attentional effects of haloperidol have been previously reported in rats. It has been shown that haloperidol given systemically impairs the sustained attention task performance by decreasing the number of behavior-initiated stimulus presentations, decreasing the number of reinforcers earned, increasing the number of errors of omission and increasing the reaction time in rats (Brockel and Fowler, 1995).

Haloperidol exerts its antipsychotic effect by blocking dopamine D_2 receptors while clozapine binds to dopamine D_4 receptors subtypes 10 times as strongly as it binds to dopamine D_2 receptors (Schotte et al., 1996). Clozapine also has been shown to have a high affinity for 5-HT_{2C} sites (in addition to the 5-HT_{2A} receptor) and a much lower affinity for dopamine D_2 sites in the cerebral cortex and striatum (Lieberman et al., 1998; Matsubara et al., 1993). Using radioligand binding assays and post-mortem normal human brain tissue, it has been shown that clozapine also binds to muscarinic and histamine receptors (Richelson and Souder, 2000). Although more studies are needed to fully understand the neuronal mechanism of clozapine on attention, it can be speculated that clozapine may exert its effect also through these neuronal systems. Similar to clozapine, risperidone also has a higher affinity for 5-HT_2 receptors than for dopamine D_2 receptor sites (Hertel et al., 1996; Sumiyoshi et al., 1994). In fact risperidone binds to 5-HT receptors 20 times stronger than it binds to dopamine D_2 receptor sites, though its binding to the dopamine D_2 receptors is comparable to that of haloperidol (Leysen et al., 1988).

Both haloperidol and risperidone have an affinity for dopamine D_2 receptors. Haloperidol's affinity for the dopamine D_2 receptors is two- to three-times stronger than that of risperidone in vitro. In addition, haloperidol administration results in quick dopamine D_2 occupancy while risperidone administration leads to gradual dopamine D_2 occupancy (Schotte et al., 1993). Because of the differences in their affinities for dopamine D_2 receptors and their effects on dopamine transmission one would expect haloperidol to exert a more pronounced impairment on cognition than risperidone. Our findings support this notion. That fact that risperidone administration decreased the number of hits on signal trials, while correct rejections remained unaffected is similar to the effect of loss of cortical cholinergic inputs on hit responding reported earlier in rats (McGaughy et al., 1996; Sarter et al., 2001). However, the exact neuronal circuits involved in hit and correct rejection responses are not fully identified. Further studies are needed to elucidate the nature of selective effect of risperidone on the hit response.

In the second experiment, nicotine–haloperidol interaction was found to be significant. Similar to Experiment 1, acute haloperidol administration caused a significant impairment in percent hit performance in the placebo infused group but failed to cause a significant effect in percent hit performance in rats chronically treated with nicotine. This observation suggests that chronic nicotine treatment prevented haloperidol-induced impairment in sustained attention at least for the first 2 weeks of nicotine treatment. The development of tolerance to the beneficial effect of nicotine after 2 weeks may present a possible limitation for its clinical use. Newly developed nicotine analogs may not have this limitation. Alternatively, nicotine might be used intermittently to avoid the development of tolerance to its therapeutic effects.

Nicotine, the principal psychoactive ingredient in tobacco products, has been shown to have a cognitive enhancement effect in rodents (Grilly et al., 2000; Mirza and Bright, 2001; Mirza and Stolerman, 1998; Muir et al., 1995; Rezvani et al., 2002, 2004; Rezvani and Levin, 2003a,b; Stolerman et al., 2000) and in healthy individuals as well as people affected by psychiatric disorders (Lawrence and Sahakian, 1995; Levin et al., 1996a,b, 1998, 2001; Peeke and Peeke, 1984; Sahakian et al., 1989; Warburton et al., 1992; White and Levin, 1999). Nicotine may enhance attention by interacting with the pre-synaptic nicotinic acetylcholine receptors to facilitate the release of acetylcholine, dopamine, serotonin, γ-aminobutyric acid, norepinephrine and glutamate (Wonnacott, 1997). Nicotine has been shown to release dopamine (Benwell and Balfour, 1997; Grenhoff et al., 1986), while classic antipsychotic drugs have been demonstrated to block dopamine transmission (Westerink, 2002). Thus, although it is likely that by promoting dopamine release nicotine can diminish the cognitive deficits associated with typical antipsychotic drugs, this has to be demonstrated.

In summary, both typical and atypical antipsychotic drugs significantly impaired sustained attention in rats as measured by choice accuracy on the visual signal detection task. Haloperidol was more detrimental in this task than clozapine and risperidone. Chronic nicotine infusion significantly diminished the impairing effects of haloperidol on performance during weeks 1–2. The rat model of sustained attention may provide a valuable approach to studying neuronal mechanisms underlying the effects of antipsychotic medications on attention. This paradigm also provides a means to evaluate the potential of novel nicotinic agonists and other agents to counteract attentional impairment.

Acknowledgements

We thank Ms. Channelle Christopher and Mr. Paul Blackwelder for their assistance in animal testing and care. We also greatly appreciate the expertise and assistance of Dr. Philip Bushnell and Mr. Charles Hamm of the US EPA in setting up our operant system. The authors also thank Ms. Ana Pocivavsek for her assistance with the project. The National Institute of Mental Health grant MH64494 supported this research.

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