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The Effects of Antipsychotic Treatment upon Nicotine Associative Reward in a Neonatal

Quinpirole Model of Schizophrenia

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## Abstract

Research has revealed that schizophrenics are significantly more likely to smoke cigarettes than the general population, and consume nicotine products at a much more prevalent rate. Further exacerbating this issue, it has been previously demonstrated in clinical populations that the type of antipsychotic treatment administered (typical versus atypical) may result in either an increase or a decrease of already heightened smoking behavior within the schizophrenic population. With these clinical issues in mind, the present study sought to examine the effects of antipsychotic treatment upon the associative reward of nicotine within the neonatal quinpirole model of schizophrenia. We found that treatment with the typical antipsychotic haloperidol blocked the associative reward of nicotine. Clozapine, an atypical antipsychotic, merely reduced the rewarding effects. These findings illustrate the centrality of the dopamine system, specifically the D2 receptor subtype, as an underlying mechanism of the rewarding effects of nicotine among rodents neonatally treated with quinpirole.

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## **Background**

### **Schizophrenia**

Schizophrenia is best and most accurately described as a progressive neurodevelopmental disorder (Khandaker et al. 2011). According to the National Institute of Mental Health, schizophrenia affects approximately 1.1 percent of individuals over 18 years of age, with symptoms usually experienced between the ages of 16 and 30 (NIMH, 2016). The NIMH further describes schizophrenia as a very severe neurodevelopmental disorder afflicting behavioral and emotive regulation with symptoms falling into three broad categories. Positive symptoms are behaviors not observed in healthy individuals and are considered to be psychotic such as delusions, hallucinations, unusual patterns of thought and movement disruptions, such as catatonia (NIMH, 2016). A second category, negative symptoms, encompasses marked disruption to normal emotions and behaviors. Examples of such symptoms include difficulty in beginning and sustaining activities, reduced speaking and anhedonia, which is a flat emotional affect. Finally, cognitive symptoms encompass changes such as poorer executive functioning, attentional deficits and impaired working memory.

The neurological underpinnings of schizophrenia are immense. While an underlying mechanism is known to be dopamine hyperactivity, other neurotransmitters have consistently been demonstrated to be interrupted. Geyer and Vollenweider (2008) have demonstrated serotonergic dysfunction, whereas Heresco (2005) demonstrated hypofunction of glutamatergic N-methyl D-aspartate (NMDA) receptors. Despite the broad neurological changes in schizophrenia, research has consistently returned to the involvement of the dopamine system, specifically the involvement of the D2 receptor. Studies have demonstrated that increased activation of the D2 receptor plays a central role in the expression of many of the abnormal

behaviors associated with schizophrenia (Adler et al. 1999, Maki et al. 2005). In addition, antipsychotic medications all target the D2 receptor with some affinity. In fact, all effective antipsychotic drugs are D2 receptor antagonists (Tollefson, 1996).

### **Modeling Schizophrenia in Rodents**

Given the clear implications of the D2 receptor type in the neuropathology of schizophrenia, it makes sense to try to encapsulate such within an animal model of schizophrenia. To this effect, our laboratory and a collaborating laboratory have consistently demonstrated that neonatal treatment with quinpirole, a dopamine D2-like agonist, produces an increase in D2 receptor sensitivity that is present across the lifetime of the animal, without a change in receptor number (Kostrzewa 1995; Brown, Gass and Kostrzewa, 2002; Brown et al., 2004; Brown et al., 2005; Brown et al., 2006; Brown et al., 2008). This increase in sensitivity parallels findings in clinical schizophrenic patients (Adler et al. 1999, Maki et al. 2005).

Critical support for the neonatal quinpirole model of schizophrenia is provided by the finding that cognitive impairment and decreased neurotrophic factor protein expression in quinpirole treated rats was alleviated by treatment with olanzapine, an atypical antipsychotic (Thacker et al. 2006). These findings parallel similar findings among human patients (Cuesta et al., 2009). Brown et al. (2012) summarized parallels between findings in the neonatal quinpirole model and in human schizophrenics, thus demonstrating several shared consistencies such as reduction in brain-derived neurotrophic factor, reductions of hippocampal ChAT expression, increased dopaminergic response to amphetamine and decreases of RGS9 protein, which regulates dopamine D2 signaling. In sum, it is clearly demonstrated that neonatal quinpirole treatment produces changes with a marked consistency to changes found in human schizophrenics.

### **Schizophrenia and Substance Abuse**

Substance abuse comorbidity is commonly encountered in major psychological disorders. Rates of substance abuse among individuals diagnosed with schizophrenia are alarmingly high. Folwer et al. (1998) estimates that approximately 60% of schizophrenic individuals suffer from substance abuse disorders concurrently. By far, the most commonly abused substance is nicotine, often in the form of smoking cigarettes. Approximately 70-80% of schizophrenic individuals are nicotine dependent (Van Dongen, 1999; Hymowitz et al, 1997; LeDuc and Mittleman, 1995). This statistic is alarmingly high compared to smoking rates of the general population. It is estimated that only one fourth of the general population smoke (Jeste et al. 1996). Beyond general consumption statistics, Lyon (1999) points out that compared to other diagnostic groups, schizophrenic patients are far more likely to be heavy smokers who smoke more than one and a half packs per day. Moreover, plasma concentrations of nicotine are higher in schizophrenic smokers than in normal smokers (Sacco et al., 2005). Given what is known about patient outlook in schizophrenia and the well documented deleterious effects of cigarette smoking, the idea of a schizophrenia and nicotine substance abuse comorbidity is particularly alarming.

Although the exact mechanism behind schizophrenia and nicotine comorbidity remains unknown, research has suggested numerous explanations. One of the more popular explanations is that the rewarding effects of nicotine use may compensate for anhedonic symptoms experienced among schizophrenic patients (Glassman, 1993). A second explanation is that smoking may eliminate several of the behavioral elements of the disorder and may compensate for some of the negative side effects of antipsychotic treatment (Le Duc, 1995). On the other hand, Winterer (2010), suggests that smoking may help attenuate the cognitive impairments associated with schizophrenia. It is important to note, however, that these views are not mutually

exclusive. In all likelihood, nicotine consumption may be used for all aspects of the disorder, and its specific usages may vary among individual patients.

### **Antipsychotic Medication Interactions with Nicotine**

Further exacerbating the already alarming nicotine abuse comorbidity is that research has consistently demonstrated that the type of antipsychotic medication administered to clinical patients may raise or lower the already heightened nicotine consumption. Haloperidol, a typical (first generation) antipsychotic is a potent dopamine antagonist which targets in particular the D2 receptor, but also the D3 and D4 receptor subtypes, with a high degree of affinity. Haloperidol has consistently been demonstrated to produce an increase in smoking among schizophrenic patients (Dawe, 1995; McEvoy, 1995; Levin 1996; Kim 2010). The exact mechanism behind this phenomena remains unknown, but Levin et al. (1996) suggest that the increase in nicotine consumption may be a compensatory mechanism for the well documented aversive effects of haloperidol. On the other hand, clozapine, an atypical (second generation) antipsychotic has demonstrated an opposite effect. Research has consistently demonstrated that patients treated with clozapine exhibit a decrease in smoking behavior (George, 1995; McEvoy, 1995). Other researchers have failed to replicate these findings, however (de Leon, 2005). Among other things, de Leon (2005) cited a lack of statistical power in earlier studies which had found an effect.

### **The Research Question**

The present study sought to directly compare haloperidol and clozapine administration in the neonatal quinpirole model as a means to determine potentially underlying mechanisms behind the variable responses to nicotine following antipsychotic treatment. Our dependent measure of interest was associative reward, which we examined using a conditioned place

preference (CPP) paradigm. For the present purpose, it was hypothesized that animals treated with haloperidol would show a greater conditioned place preference to the context in which nicotine was administered, thus demonstrating associative reward.

### **Experimental Design and Procedure**

In order to examine the effects of antipsychotic treatment upon nicotine associative reward, a 2X2 factorial design was used. Neonatal drug treatment (quinpirole or saline) and adolescent drug treatment (haloperidol or clozapine) were manipulated factors. Our dependent measure, associative reward, was measured using a conditioned place preference paradigm (CPP). Conditioned place preference is heavily rooted in Pavlovian conditioning and measures the associative learning that has occurred between a stimulus and the context in which it was received. The importance of environmental cues in drug conditioning has been consistently demonstrated in research. Specifically, in studies involving nicotine addiction, the importance of environmental cues has been demonstrated both in clinical and in preclinical models (Caggiula, et al. 2001; Palmatier et al. 2006).

A sample size of 27 male Sprague Dawley rats were neonatally treated with either quinpirole or saline (control) until post-natal day (P) 21. Animals were then raised to P41 without further drug treatment. From P41- 42, animals were given a drug free pre-test in a conditioned place preference apparatus. The apparatus consists of three chambers of identical dimension separated by partitions. Tactile and visual cues vary between the chambers (Figure 1). Partitions were removed during the pre-test in order to allow the animal to freely explore. Each trial was ten minutes in length. The time spent in each context over the two-day period was averaged in order to determine each animal's favored context.



Conditioning trials began on P43, and concluded on P50. Conditioning periods occurred twice daily, once in the morning at approximately 10 am, and once in the afternoon, at approximately 2 pm. Each conditioning period lasted ten minutes. During the morning

conditioning period, subjects were

intraperitoneally (ip) administered acetic acid

(pH 6-7) as a control substance. A period of 10

minutes occurred between each administration

and trial. Acetic acid was chosen as a control

substance because it served as the vehicle for

antipsychotic administration during the afternoon conditioning



Figure 1: Conditioned Place Preference Chamber

period. Conditioning during the afternoon period occurred in the opposite context to each

subject's initial preference. If no preference was demonstrating during pre-test, the subject was

randomly assigned. Subjects were ip administered haloperidol (.5mg/kg) or clozapine (2.5

mg/kg). The dosages used correspond to clinically relevant dosages. Twenty minutes following

this initial administration, subjects were ip administered a 0.6 mg/kg (free base) dose of nicotine.

Conditioning in the chamber occurred ten minutes following nicotine administration

A drug free post-test occurred on post-natal day 51. During this period, subjects were

administered pH-adjusted acetic acid and allowed to freely explore the apparatus. Throughout

the duration of the 11 day experiment, animal movement was recorded with AnyMaze behavioral

tracking software (Stoelting, Wood Dale, IL). As a measure of associative learning, a difference

score was computed between time spent in the conditioned context between pre-test and post-

test. Ambient lighting was checked between each trial to ensure consistency and to control for

any confounding factors.

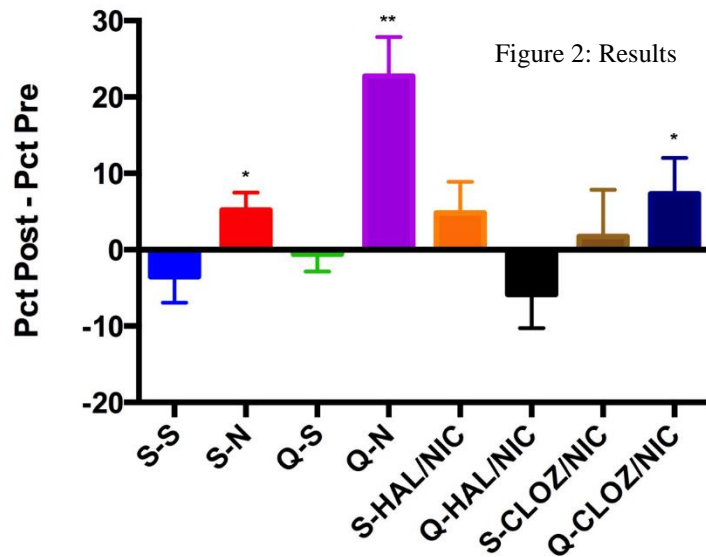
## Results

Statistical analysis revealed a main effect of adolescent drug treatment upon conditioned place preference  $F(1)=4.36$ ;  $p=0.010$ . A significant interaction effect was found between neonatal drug treatment and adolescent drug treatment  $F(3)=3.23$ ;  $p=0.033$ , which demonstrated a clear effect of antipsychotic

medication upon nicotine associative reward in rats neonatally treated with quinpirole. Animals neonatally treated with saline did not exhibit a statistically significant interaction effect of antipsychotic medication upon nicotine associative reward. As

expected, no main effect of neonatal drug treatment was observed  $F(1)=1.71$ ;  $p=0.199$ . Animals pre-treated with clozapine prior to nicotine demonstrated a reduction in conditioned place preference. This is expected as it is consistent with research using human schizophrenic patients conducted by McEvoy et al. (1995), who demonstrated a decrease in smoking behavior prior to daily treatments with clozapine.

Haloperidol, surprisingly, completely abolished nicotine conditioned place preference. This finding serves as a departure from findings in clinical literature, as haloperidol has consistently been demonstrated to increase nicotine consumption among schizophrenic patients (McEvoy et al., 1995; Levin et al., 1996). The results, along with data from earlier CPP work for comparison, are displayed in figure 2. As clearly demonstrated by the data represented in the



figure, the effect of haloperidol upon nicotine conditioned place preference is quite robust. Haloperidol administration reduced nicotine conditioned place preference to control levels. This finding is impressive considering the consistently robust conditioned place preferences for nicotine in rodents treated with quinpirole.

### **Discussion and Significance**

Despite the fact that these results failed to confirm our initial hypothesis, they reveal important information. The finding that haloperidol completely abolished nicotine conditioned place preference is quite sensible considering its pharmacokinetics. Haloperidol antagonizes the dopamine system, particularly the D2, D3 and D4 receptors, with very high affinity. Given that quinpirole treatment results in a supersensitivity of D2-like receptors (Kostrzewa, 1995), and that the clear underlying dopaminergic misregulation is involved in the rewarding effects of nicotine, these results very clearly highlight the overall importance of the dopamine system, in particular the D2 receptor, in nicotine and schizophrenia comorbidity. Compared with haloperidol, clozapine does not block the D2 receptor with the same affinity, and is overall a less potent dopamine antagonist. Thus, these findings add support to the involvement of the dopamine system in nicotine use among schizophrenic patients.

Beyond these findings, however, the question still remains as to why the results do not parallel the clinical literature. As mentioned, studies among schizophrenic patients demonstrate that haloperidol actually serves to increase nicotine consumption (McEvoy et al., 1995). The likely explanation as to why our findings do not parallel the clinical literature is found in the measure that was used. The mechanism behind nicotine use increases in patients administered haloperidol is likely not contextual by nature, and thus would not necessarily be detected by a conditioned place preference paradigm, which measures associative reward. Thus, it would

appear from this study that the actual mechanism behind the increase in smoking observed in patients treated with haloperidol is much more direct in action. The specific nature of this mechanism requires further study.

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