A D2 Antagonist Enhances the Rewarding and Priming Effects of a Gambling Episode in Pathological Gamblers

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Table of Contents

List of Figures

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Abstract

This study examined effects of the selective dopamine D2 antagonist, haloperidol (3-mg, oral) on responses to actual gambling (15-minutes playing a slot machine) in 20 non-comorbid pathological gamblers and 18 non-gambler controls in a placebo-controlled, double blind, counterbalanced design. In Gamblers, haloperidol significantly increased self-reported rewarding effects of gambling, post-game priming of desire to gamble, facilitation of reading speed to Gambling words, and gambling-induced elevation in blood pressure. In Controls, haloperidol augmented gambling-induced elevation in blood pressure, but had no effect on other indices. The findings provide direct experimental evidence that the D2 substrate modulates gambling reinforcement in pathological gamblers.

Key words: gambling, dopamine, D2, haloperidol, reward, priming

Introduction

Pathological gambling is a psychiatric disorder that often can incur devastating consequences. Evidence on the neurochemical mediators of the rewarding or reinforcing effects of gambling activity itself has just begun to emerge. Recent functional Magnetic Resonance Imaging (fMRI) research found that a gambling-like guessing game activates the mesolimbic reward system in pathological gamblers and controls (Reuter, Raedler, Rose, Hand, Glascher, & Buchel, 2005). Research that employed a cross-priming strategy found that d-amphetamine, a non-specific dopamine agonist, selectively primes motivation to gamble in pathological gamblers, indicating shared neurochemical substrates for gambling and psychostimulant reward (Zack & Poulos, 2004). This suggests that, as in the case of psychostimulants, activation of specific dopamine substrates may directly govern the reinforcement process in pathological gambling. Evidence on this issue is critical for understanding gambling's addictive-like effects in vulnerable individuals. Given the importance of the dopamine D2 receptor in genetic risk for pathological gambling (Comings et al., 1996), this study examined the effects of the selective D2 antagonist, haloperidol, on responses to a brief episode of gambling in pathological gamblers and healthy controls.

Method

Subjects

Twenty (3 female) non-treatment seeking pathological gamblers, with no co-morbidity on screening tests, and 18 (4 female) healthy controls, were recruited by newspaper advertisements and paid for participation. Gamblers were explicitly advised that the study was not intended to treat their gambling problems. All subjects underwent a physician's exam prior to testing. Sample age was 21-64 (M = 38.9, SD = 11.7) years. There were no group differences on any demographic variables. Neither group showed clinically relevant elevations in anxiety, depression, alcohol use, or drug abuse. Mean (SD) drinks/week were 2.8 (2.4) for Gamblers and 1.6 (1.9) for Controls. Mean (SD) scores on the Beck Depression Inventory-short form (Beck & Beck, 1972) were 3.6 (3.1) for Gamblers and 1.1 (1.9) for Controls.

All Gamblers scored ≥ 5 (M = 11.0, SD = 4.4) for Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV) Pathological Gambling (American Psychiatric Association, 1994). Their gambling expenses were substantial. Mean (SD) weekly expenditure on gambling was $279 (266), corresponding to 20.3 % (12.4) of their income, with an average maximum loss on a single occasion of $7,563 (22,179). Controls all scored 0 on the DSM-IV, spent $1.0 (1.3) per week on gambling, and reported an average maximum loss on a single occasion of $7.1 (8.4). Thus, Controls were essentially non-gamblers. Among Gamblers, regular gambling activities were: casino games (15/20), slots (12/20), sports (8/20), horseracing (6/20), lottery (4/20), and bingo (1/20).

Scales and Apparatus

Modified visual analog scales (m-VAS; 0-10) measured subjective-motivational effects of gambling and perceived effects of the capsule (Good Effects, Bad Effects, and Desire to Take Again). The Addiction Research Center Inventory (ARCI; Haertzen, 1965) provided a complementary standardized measure of drug effects.

A rapid reading task (Lexical Salience Task) measured reading reaction time (in ms) to degraded Gambling words (e.g., w*a*g*e*r) versus Neutral words (e.g., w*i*n*d*o*w). The task and stimuli are identical to those detailed in a previous study (Zack & Poulos, 2004). Salience is operationally defined as the difference in reading latency to Gambling versus Neutral words.

A commercial slot machine currently used in Ontario casinos ("Cash Crop"; WMS Gaming, Chicago, IL) served as the motivational prime. Subjects could wager 1-45 credits/spin, and were told that they would receive a monetary bonus proportional to their final credit tally from each session.

Blood pressure was assessed with an automated wrist cuff (HEM-601 Omron Inc, Vernon Hills, IL).

Procedure

After providing informed consent, subjects attended 2 test sessions, 1-week apart, where they received 3-mg oral haloperidol or placebo in a double blind, counterbalanced design. Haloperidol (3-mg, oral) induces 60-70% D2 receptor occupancy and reaches peak blood levels at 2.75 hours post-administration (Nordstrom, Farde, & Halldin, 1992).

On each test session, 2.75 hours after dosing, subjects engaged in 15 minutes of gambling on the slot machine with $200 in credits in a mock-bar laboratory. Subjective effects and blood pressure were assessed at pre-capsule (baseline) and throughout the test session. The Lexical Salience Task was administered immediately after gambling.

To minimize possible residual priming effects of the slot machine, subjects remained at the laboratory for 4 hours after testing was completed. They were assessed by a registered nurse prior to dismissal and sent home by pre-paid taxi. Upon dismissal, subjects received a sealed 50-mg dose of diphenhydramine (Benadryl®) to use in the event of a delayed dystonic reaction.

Data Analytic Approach

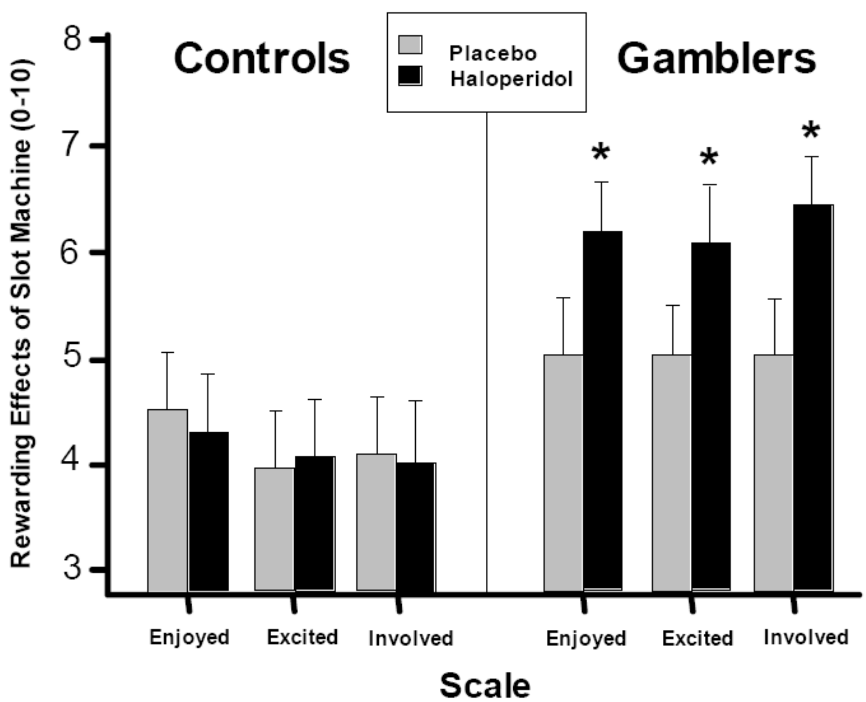
Analyses of covariance isolated Treatment effects (Wainer, 1991), while controlling for pre-capsule group differences on pertinent indices (e.g., Desire to Gamble). ANOVA's were used for indices with no pre-capsule measurements.

Results

Mean (*SD*) m-VAS ratings of the capsule's "Bad Effects" were modest, but significantly greater under haloperidol, 0.7 (1.9) than placebo, 0.2 (1.9), $p < .05$, with no group effects or interaction. Neither the ARCI nor the other visual analog ratings of drug effects yielded any significant effects.

Figure 1 shows mean (*SEM*) ratings of gambling-induced Enjoyment, Excitement, and Involvement. Haloperidol increased scores on each sub-scale in Gamblers, *p*'s < .001, but had no significant effect in Controls. (Mean shared variance across sub-scales: Gamblers, $r^2 = 0.66$, Controls $r^2 = 0.65$).

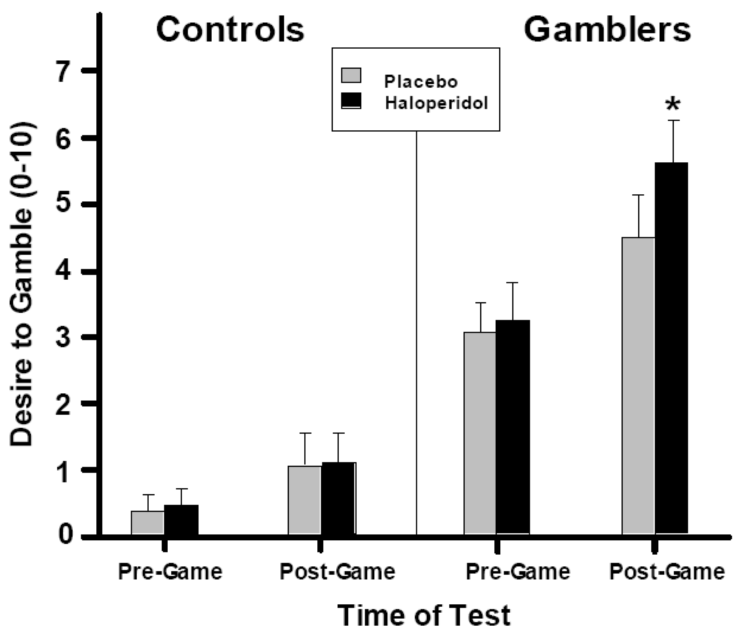
<u>Figure 1</u>. Mean (*SEM*) self-reported pleasurable effects of a 15-minute slot machine game in pathological gamblers ($n = 20$) and controls ($n = 18$) under haloperidol (3-mg, oral) and placebo.



* Drug treatment effect, $p < .001$.

Figure 2 shows Desire to Gamble ratings before and after gambling. Haloperidol had no effects on pre-game Desire in either group. Gambling itself primed Desire in both groups under placebo, *p*'s < .001. Haloperidol augmented this priming of Desire in Gamblers, $p < .001$, but not in Controls.

<u>Figure 2</u>. Mean (*SEM*) self-reported desire to gamble before and after a 15-minute slot machine game in pathological gamblers ($n = 20$) and controls ($n = 18$) under haloperidol (3-mg, oral) and placebo.



* Drug treatment effect, $p < .001$.

On the Lexical Salience Task, haloperidol significantly improved relative reading speed to Gambling versus Neutral words in Gamblers but not in Controls. Specifically, in Gamblers, mean (*SD*) reading speed was 895 (261) ms to Gambling words versus 1,036 (349) ms to Neutral words under haloperidol (salience difference = 141 ms), as compared to 950 (366) ms to Gambling words and 1,064 (402) to Neutral words (salience difference = 115 ms) under placebo, $p < .05$. Controls showed no significant difference in relative reading speed to Gambling words, 998 (237) ms versus Neutral words, 1,147 (319) ms (salience difference = 149 ms) under drug, compared to 1,060 (239) ms to Gambling words and 1,221 (359) ms to Neutral words (salience difference = 161 ms) under placebo. Thus, in Gamblers, haloperidol significantly augmented the relative salience of Gambling words following the slot machine, but had no effect in Controls.

Figure 3 shows the effects of the slot machine game on systolic blood pressure (mm Hg) under haloperidol and placebo in Controls. Figure 4 shows the corresponding scores for Gamblers.

Figure 3. Mean (*SEM*) systolic blood pressure (mm Hg) at pre-capsule baseline and at 30-minute intervals before and after a 15-minute slot machine game in healthy control subjects (*n* = 18) under haloperidol (3-mg, oral) and placebo.

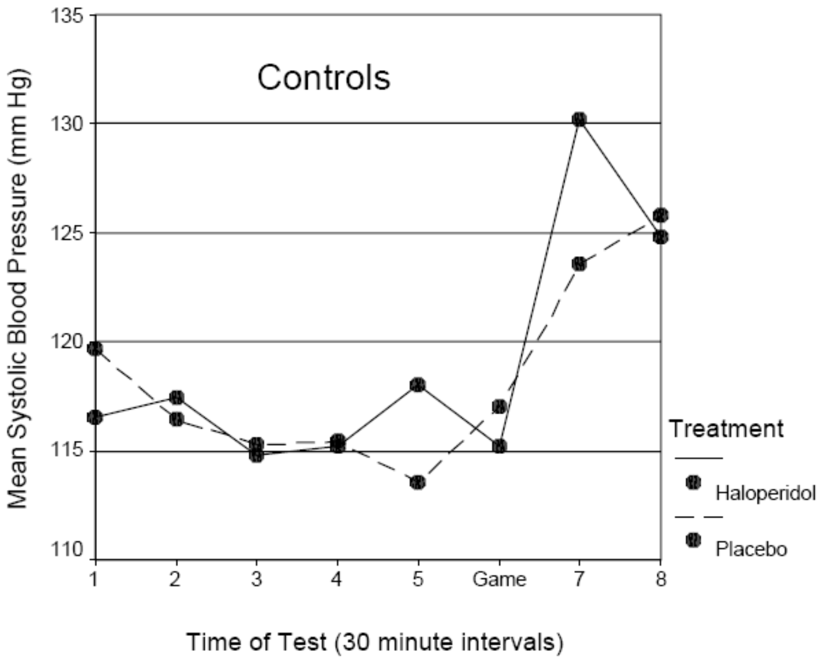
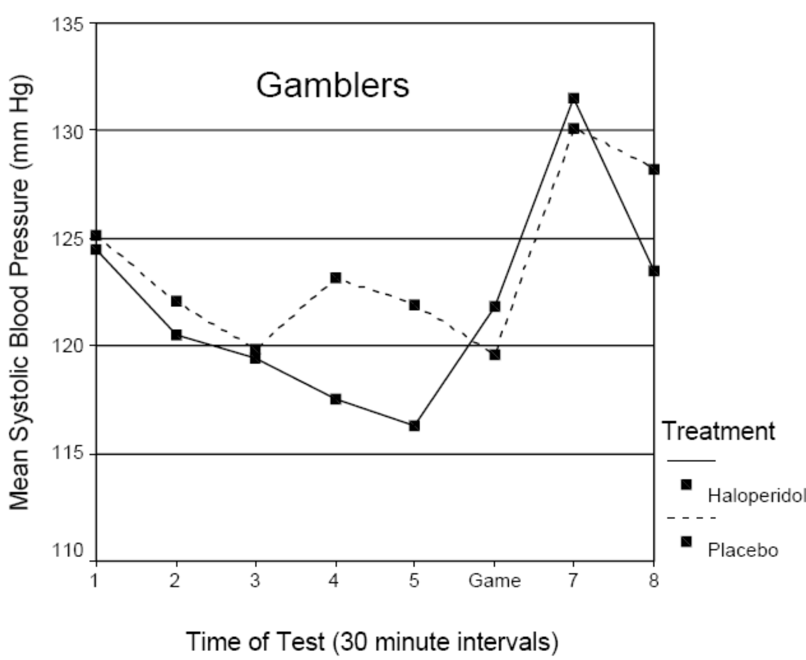


Figure 4. Mean (*SEM*) systolic blood pressure (mm Hg) at pre-capsule baseline and at 30-minute intervals before and after a 15-minute slot machine game in pathological gamblers (*n* = 20) under haloperidol (3-mg, oral) and placebo.



As indicated, the slot machine induced a significant increase in systolic blood pressure in both groups under placebo, *p*'s < .001. Comparison of pre-game minimum scores with post-game scores in each figure indicates that the pre-post gambling increase in systolic blood pressure was greater under haloperidol than placebo for both groups, *p*'s < .01.

There were no significant effects involving Group or Treatment on slot machine play for mean (*SD*) credits bet/spin, 13.1 (7.1), maximum credits bet/spin 29.4 (10.1), or final credits earned 409.6 (419.6). Gamblers played more spins/game, 89.4 (39.4) than Controls, 60.6 (41.6), $p < .01$, but this did not vary with Treatment.

Discussion

Haloperidol increased the rewarding, priming, and physiological activating effects of gambling in pathological gamblers. Effects were clear and convergent across self-report, Lexical Salience Task, and blood pressure indices. Blood pressure data indicated that haloperidol also enhanced the activating effect of gambling in Controls, although there was no corresponding effect on other indices. Thus, in Control subjects, who were essentially non-gamblers, haloperidol enhancement of physiological activation appears to be dissociated from gambling reinforcement.

That partial D2 blockade should enhance gambling reinforcement in pathological gamblers may seem somewhat surprising. However, the findings are consonant with those of Positron Emission Tomography (PET) studies by Volkow et al. (2002), which found an inverse correlation between D2 receptor availability and subjective rewarding effects of the psychostimulant methylphenidate in healthy volunteers. The present findings also parallel an earlier *paradoxical* finding that pre-treatment with 2-mg of the D2 antagonist, pimozide, increased discriminability and "liking" of d-amphetamine in volunteers (Brauer & de Wit, 1996).

As noted, genetic studies have proposed that low D2 receptor function is a key risk factor for the development of pathological gambling (Comings et al., 1996). The present findings provide experimental evidence for a mechanism that may mediate this association. Given the apparent neurochemical similarity between gambling and psychostimulant reinforcement (Zack & Poulos, 2004), the present findings suggest that other dopamine substrates that interact with D2, and influence psychostimulant reinforcement (D1 and D3 receptors; Xu, 1998), could well be important for gambling reinforcement. Finally, the present findings suggest that drugs that enhance dopamine transmission at the D2 substrate may be promising candidates for investigating as medications for pathological gambling.

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