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Systemic injection of the DAD1 antagonist SCH 23390 reduces saccharin seeking in rats

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Abstract

Conditioned cues can elicit drug- and sucrose-seeking behaviors that have been shown to depend on dopamine (DA) D1 receptors. If DAD1 receptors are also involved in seeking behavior in general, blocking these receptors should reduce seeking behavior for a non-caloric, non-drug of abuse reinforcer such as saccharin. Forty-six male Long-Evans rats lever pressed for 0.3% saccharin solution 1 h/day for 10 days. A lever response also activated a tone plus a white stimulus light. This compound stimulus lasted for 5 seconds. After 1 day of forced abstinence, rats received systemic (0, 1, or 10 µg/kg IP; n=15–16 per group) injections of SCH 23390 15 minutes prior to extinction testing. Systemic SCH 23390 reduced saccharin seeking evidenced by a significant reduction in active lever responding and a significant reduction in the number of active lever-contingent deliveries of the tone+light cue following pretreatment with 10 µg/kg SCH 23390. The slope of responding across the Test session in this group was also significantly steeper, indicating that SCH 23390 may have reduced the persistence of saccharin seeking. The results indicate that DAD1 receptors are involved in saccharin seeking and generalize the previously demonstrated anti-seeking effects of DAD1 antagonism to a non-caloric, non-drug of abuse reinforcer.

Keywords

addiction; craving; saccharin; dopamine; SCH 23390

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Introduction

Craving characterizes individuals with substance abuse disorder and overweight or obese patients attempting to lose weight (e.g., Mendelson and Mello, 1996; Grodstein et al., 1996). Conditioned cues can elicit craving (Sobik et al., 2005; Epstein et al., 2009). Cue-induced seeking behavior (cue-reactivity) is often used as an animal model of craving. In the past, most studies using this model to better understand food craving behavior focused on high calorie foods such as sugar (e.g., Grimm et al. 2011) or fat (e.g., Nair et al. 2009). This seems reasonable because consumption of these foods should contribute to the development of weight gain and perhaps obesity. However, consumption of non-caloric, high-intensity sweeteners could also contribute to increases in body weight. For example, it has been repeatedly demonstrated that when free-feeding rats were given the non-caloric sweetener saccharin, they gained more body weight than when they were given the high-caloric sweetener glucose (see Swithers et al. 2010 for review). These days, non-caloric, high-intensity sweeteners are substituted for added sugars in a wide variety of foods and this means that millions of people are consuming these sweeteners daily, often with a goal of reducing body weight. Therefore, understanding of seeking behaviors for a non-caloric sweetener could be important to better understand how these sweeteners may or may not improve control over body weight.

The non-nutritive, highly-sweet reinforcer saccharin is the prototypical reinforcer for such studies. The neurobiology of saccharin seeking may be better understood using a behavioral pharmacology approach. Craving, assessed in rodent models such as with cue-reactivity, is partly mediated by the mesolimbic motivational pathways. This goal-directed, dopamine (DA)-mediated behavior could be described as “wanting” in incentive motivation theory (Berridge et al., 2009) and as heavily affected by DA-mediated “effort” in another motivation-based theory of reinforcement (Salamone et al. 2015). Regardless of the theoretical underpinning, cue-reactivity for a variety of reinforcers has been shown to involve DAD1 receptors (e.g., contextual cues, Crombag et al., 2002; discrete cues, Grimm et al., 2011). If DAD1 receptors are involved in craving behavior in general, blocking these receptors should also reduce seeking behavior for the non-caloric, non-drug of abuse reinforcer saccharin. Therefore, we examined the effects of systemic administration of the DAD1 antagonist SCH 23390 on saccharin seeking in rats with a history of saccharin self-administration. This was the primary aim of the present study.

A secondary aim was to analyze the within-session pattern (e.g., McSweeney and Murphy, 2014) of saccharin seeking following SCH 23390. Recently, we investigated the within-session changes in saccharin or sucrose seeking in the absence of drug challenge (Aoyama et al. 2014). We found that a linear equation that had been previously applied to the within-session changes in responding for primary reinforcers (e.g., food) could describe those for secondary reinforcers (i.e., saccharin or sucrose seeking, Aoyama et al.). In addition, we found that the incubation of craving (Grimm et al. 2001) for either reinforcer was related to changes in parameters of the linear equation that may be indicative of changes in persistence and vigor of responding. It was hypothesized that if SCH 23390 were to alter response rate for a saccharin-paired cue during a saccharin-seeking test, this change would be reflected in a change in parameters of the linear equation describing the within-session responding. If so,

this would provide a richer understanding of the role of DAD1 receptors in cue-reactivity, at least in the case of saccharin seeking.

Methods

Subjects

Sixty male Long-Evans rats (3 months old at the start of study; Simonsen-derived) were housed individually on a reverse day/night cycle (lights off at 7 AM) with nutritionally balanced Purina Mills Inc. Mazuri Rodent Pellets (Gray Summit, MO, USA) and water available *ad libitum* except as noted below. Pellets and water were freely available in the operant conditioning chambers, except as noted below.

Saccharin solution was provided for 48 hours in the home cage before water deprivation to facilitate subsequent saccharin self-administration (SA). Immediately prior to the SA Training phase, the animals were deprived of all liquid for 17 hours to encourage SA on the first day of training. Rats were then returned to *ad libitum* water access. Procedures followed the guidelines outlined in the PHS “Policy on Humane Care and Use of Laboratory Animals” (PHS 2002) and were approved by the Western Washington University IACUC.

Apparatus

Operant training and testing took place in operant conditioning chambers (30 × 20 × 24 cm; Med Associates) containing two levers (one stationary and one retractable), a tone generator (2 kHz, 15 dB over ambient noise), a white stimulus light above the retractable lever and a red house light on the opposite wall. An infusion pump delivered saccharin into a receptacle to the right of the active lever. Four infrared photobeams crisscrossed the chamber. Operant conditioning chambers were enclosed in sound-attenuating cabinets with ventilation fans.

Procedure

Training phase—Rats spent 1 hour/day for 10 consecutive days in the operant conditioning chambers where they were allowed to press the retractable (active) lever for 0.2 ml delivery of 0.3% saccharin. An active lever response also activated a compound stimulus consisting of the tone and the white light. This compound stimulus lasted 5 seconds and was followed by a 40-second time out, during which presses were recorded but had no consequence. A response on the inactive lever did not have a consequence, but was recorded. The total number of photobeam breaks was recorded in each session. After each session, rats were returned to home cages. Water was provided in the operant conditioning chambers once rats reliably responded for saccharin (≥ 20 deliveries/day). All rats received acclimatization saline injections the two afternoons prior to their test day. At the end of the Training phase, rats ($n = 15$ or 16 rats/group) were assigned to one of three conditions (0, 1, or 10 $\mu\text{g/kg}$ IP injections of SCH 23390). Active lever responses were matched between groups to ensure groups did not significantly differ during training.

Testing phase—On the day following the Training phase, rats were tested in the operant conditioning chambers for saccharin cue-reactivity (saccharin seeking). This session was identical to the 1-h Training procedure, but saccharin was not delivered following a lever

response. The DAD1 antagonist SCH 23390 (Sigma, St. Louis, MO, USA) was dissolved in sterile saline. The drug was injected 15 min prior to a test session (0, 1, or 10 µg/kg IP). Only one test was conducted for each rat.

Statistical Analyses

Training Phase—Average active lever responses, reward deliveries, inactive lever responses, and photobeam breaks during the final 4 days of training were analyzed separately using analysis of variance (ANOVA). The DOSE of SCH 23390 (0, 1, or 10 µg/kg) was used as a between-group factor.

Testing Phase—The effects of SCH 23390 on active lever responses, cue-presentations, inactive lever responses, and photobeam breaks were evaluated separately using ANOVA. Post hoc comparisons were made with Tukey HSD tests.

Within-Session Changes in Active Lever Responses—The test sessions were divided into 6, 10-minute blocks. First, group response rates (number of active lever responses per minute) were described as a function of time blocks. Within-session changes in responses were analyzed by a two-way RM ANOVA using TIME-BLOCKS (blocks 1 to 6) and the between-group factor DOSE (0, 1, or 10 µg/kg). Second, response rates were described as a function of cumulative number of cue presentations. A linear regression line (Eq. 1) was then calculated separately for each group.

The linear equation appears as

$$R_r = a - b I_c \quad (\text{Eq. 1})$$

where I_c is cumulative number of reinforcer deliveries, a and b are free parameters, and R_r is response rate. Response rate stands for number of responses per unit time. Parameter a is the y -axis intercept of the regression line. This parameter indicates response rate at the beginning of the session. Parameter b is the slope of the regression line. This parameter represents the rate of response decrease produced by a single presentation of a reinforcer. As noted above, this equation has been fit to within-session responding for either primary (Aoyama, 1998) or secondary reinforcers (Aoyama et al. 2014). Aoyama et al. (2014) hypothesized that for seeking behavior (responding for secondary reinforcement) the y -axis intercept (parameter a) may represent vigor of seeking behavior and that the slope (parameter b) may indicate persistence of seeking behavior.

A linear regression line, using Eq. 1, was then calculated for each subject. The resulting parameters (y -axis intercepts, x -axis intercepts, slopes, and r^2 s) were then compared between groups using ANOVA.

Results

Fourteen rats were removed from the study because they did not meet an acquisition criterion of an average of 20 saccharin deliveries/day over the last 4 days of training. Final group sizes were 16 for the saline group and 15 for the each of the 1 µg and 10 µg groups.

Training Phase

Training data are depicted in Figure 1. There were no significant differences between groups for all dependent variables over the final 4 days of Training.

Testing Phase

Figure 2 shows the average number of active lever responses, cue presentations, inactive lever responses, and photobeam breaks during the Testing phase. For active lever responses, there was a statistically significant main effect of DOSE, $F(2,43) = 3.9$, $P < .005$. Post hoc comparison revealed that the 10 µg group responded significantly less than the saline group. For cue presentations, there was a statistically significant main effect of DOSE, $F(2,43) = 6.3$, $P < 0.01$. Post hoc comparisons revealed that the 10 µg group responded for significantly fewer cue presentations than the saline and the 1 µg groups. There were no significant differences in inactive lever responses or photobeam breaks between the three groups of animals.

Within-session Changes in Responding During the Testing Phase

Figure 3 presents the mean response rate during successive 10-min blocks in the Testing phase. Active lever responses decreased during the test session with TIME-BLOCK, $F(5,215) = 54.3$, $P < 0.001$. In addition, the main effect of DOSE was also significant, $F(2, 43) = 3.9$, $P < 0.05$. Post hoc comparisons revealed that the 10 µg group responded significantly less than the saline group throughout the test session. The interaction between TIME-BLOCK and DOSE was not significant, $F(5, 130) = 0.7$.

Figure 4 presents the mean response rates of each treatment group as functions of cumulative number of cue presentations for the 3 treatment conditions. There was a linear relationship between mean response rates and cumulative numbers of cue presentations, $r^2s > .84$, for each treatment condition. After fitting the data from individual animals to Eq. 1, the resulting y -axis intercepts, slopes, x -axis intercepts, and r^2s were compared between the 3 treatment conditions using ANOVA. The main effect of DOSE was marginally significant for slope, $F(2, 43) = 2.9$, $P = 0.067$ and x -axis intercept, $F(2, 43) = 3.1$, $P = 0.053$. The main effect of DOSE was not significant for y -axis intercepts, $F(2,43) = 0.06$, $P = 0.54$, and r^2 , $F(2, 43) = 0.5$, $P = 0.62$.

Table 1 indicates the parameters of the regression lines (Eq. 1) when the equation was applied to individual subjects. As shown in the Table, the regression line explained the within-session changes in responding, indicated by a statistically significant fit, $P < 0.05$, in a majority (59%) of the subjects. However, the behavior of a significant number of subjects (41%) could not be accounted for by the equation.

Discussion

This study showed that systemic SCH 23390 reduced saccharin seeking after 1 day of forced abstinence evidenced by a significant reduction in active lever responding and a significant reduction in the number of active lever-contingent deliveries of the tone+light cue following pretreatment with 10 µg/kg SCH 23390. These findings generalize the previously described anti-cue-reactivity (seeking) effects of systemic SCH 23390 from sucrose (Grimm et al., 2011), cocaine (Koob et al., 1996), and nicotine (Liu et al., 2010) to a non-drug, non-caloric palatable reinforcer. We believe these findings to be the first report of this kind.

There was no effect of SCH 23390 on inactive lever presses or on general locomotor activity. Thus, systemic SCH 23390 did not cause a general motor impairment. We conclude that DAD1 receptors are involved in saccharin seeking and generalize the previously demonstrated anti-craving effects of DAD1 antagonism to a non-caloric, non-drug of abuse reinforcer. This is not a surprising effect given that DAD1 antagonism has been found to decrease cue-reactivity for several other reinforcers (food and drug, noted above), suggesting that DAD1 receptors are involved in cue-reactivity in a general sense, regardless of reinforcer type. The effect with saccharin is novel, however, and also important to consider for at least two reasons. First, as described in the Introduction, non-nutritive sweeteners including saccharin could actually increase calorie intake by humans (Swithers et al. 2010). This could be due to a duality in the neuronal substrates signaling hedonic and caloric aspects of sucrose within the mesolimbic reinforcement circuitry (Tellez et al. 2016). Perhaps saccharin sweetness, not matched with caloric value, leads to a compensatory increase in caloric need. Second, non-nutritive sweeteners such as saccharin serve as powerful reinforcers outright. Recent evidence with rats shows that the reinforcing effects of saccharin sweetness may, in some contexts, surpass that of drugs of abuse, including cocaine and heroin (Madsen and Ahmed, 2015). Therefore, exploring the neurobiology of saccharin seeking could provide important information for understanding the neurobiology of reinforcement in general.

Interestingly, a recent study found that SCH 23390 reduced ultrasonic anticipatory calls in response to food cues by rats (Buck et al., 2014). Together with our observation that SCH 23390 significantly reduced overall response rate for saccharin-paired cues, and along with several other findings where DAD1 antagonism reduced responding for sucrose and drugs of abuse (Grimm et al., 2011; Liu et al., 2010; Weissenborn et al., 1996), these findings point to DAD1 antagonism reducing the motivation to respond to (or for) reward-paired cues. These effects may contributed to a better understanding of how saccharin-paired cues, and cues paired with other reinforced behaviors, affect motivated responding such as craving. Further study is needed to better understand the particular aspect of motivation (e.g. wanting Berridge et al., 2009 or effort Yohn et al., 2015) affected by DAD1 antagonism.

To this end, we applied Eq. 1 to the within-session changes in responding for a cue associated with saccharin. The linear relationship between mean response rates and cumulative number of saccharin cue presentations were generally high; r^2 s were 0.84 for saline, 0.90 for 1µg, and 0.87 for 10 µg groups. Thus, we replicated the finding that within-session changes in active-lever responses for a secondary reinforcer could be described as a

linear function of cumulative number of cue presentations. However, SCH 23390 did not significantly affect the various parameters of Eq. 1. As noted above, we previously suggested that the slope (parameter b) may indicate persistence of seeking behavior. There was a marginally significant effect of SCH 23390 on slope ($P = 0.07$), with slope in the 10 μg dose group being steepest (visual inspection of Figure 3). It is possible that SCH 23390 has an effect of reducing persistence of seeking behavior, but likely due to variability in within-session responding across animals (Table 1) we did not have the statistical power to establish this with certainty. Inspection of the group variance (S^2) for slope within each treatment condition supports this hypothesis with S^2 in the drug-treated groups being much higher than in the saline-treated group. For the 10 μg dose condition, S^2 was approximately 11 times larger (S^2 values: saline = 0.05, 1 μg dose = 0.14, 10 μg dose = 0.55). This increased variability could indicate that rats have individual sensitivities to D1 antagonism and/or that the DAD1 antagonism is affecting some other behavior or behavioral state that we are not yet aware of.

To explore this further, we examined how individual differences in Training behavior might account for within-session patterns of responding during Testing. The Training behavior examined was probability of reinforcement. This was calculated by dividing the number of reinforced active-lever responses by the total number of active-lever responses. Individual differences are found with this measure as some rats respond more during the 40-sec timeout period. More responding during the timeout would result in less probability of reinforcement. Similar measures have been used previously to predict individual differences in drug-seeking behavior (e.g. Kruzich et al., 1999). Probability of reinforcement over the last four days of training did not differ between the three groups that were subsequently to be treated with different doses of drug ANOVA $F(2,43) = 0.61$, $P = 0.55$. Probability of reinforcement for each subject was then correlated with individual parameters of fit to Eq.1. There were significant correlations between probability of reinforcement over the last four days of training and slope: $r = -.43$, $P < 0.01$ and y-axis intercept: $r = -.63$, $P < 0.01$ during cue-reactivity testing. Probability of reinforcement was not found to be significantly correlated with either x-axis intercept or r^2 . As this exploratory analysis revealed probability of reinforcement to be a likely source of the variability observed in the initial comparison of Eq.1 parameters between drug-treatment conditions, the ANOVA was re-calculated using probability of reinforcement as a co-variate (ANCOVA). When controlling for the influence of probability of reinforcement, DOSE was statistically significant for slope $F(1,42) = 4.7$, $P < 0.05$ and marginally significant for x-axis intercept $F(1,42) = 3.0$, $P < 0.06$. Bonferroni post hoc comparisons for slope revealed a significant difference between the saline and 10 μg SCH 23390 conditions, $P < 0.05$. This finding provides more support for this DAD1 antagonist affecting how quickly rats reduce their responding for a reward-paired cue. As discussed above, the steeper slope parameter in the 10 μg condition may indicate a decrease in the persistence of seeking behavior. Previous studies demonstrating that SCH 23390 reduced cocaine seeking also concluded that the drug had a selective effect on persistence, as opposed to initiation of responding or general motor impairment (Alleweireldt et al. 2002; Quick et al. 2011). The present study therefore extends these findings, derived using a novel statistical method, to a non-drug reinforcer.

Further study is needed to reveal in more detail how individual differences in previous reward taking (saccharin or other rewards) affect how an individual subsequently responds for reward-paired cues. Furthermore, it would be important to identify how those individual predispositions might predict an individual's response to a pharmacological challenge. This would be relevant to development of precision medicine for addiction-related behaviors such as craving (van der Stel, 2015).

Finally, several laboratories have identified brain regions that subserve these effects of SCH 23390. For example, Grimm et al. (2011) and Guy et al. (2011) observed decreased sucrose seeking with SCH 23390 administered to nucleus accumbens subregions. Similar decreases have been reported for morphine (Gao et al., 2013) and heroin (Bossert et al., 2007) seeking. The prelimbic cortex (heroin; See, 2009) and basolateral amygdala (cocaine; See et al., 2001) are other regions where SCH 23390 reduces seeking behavior. Further study is needed to examine the possible generality of these site-specific effects of SCH 23390 to saccharin seeking. Overall, the fact that SCH 23390 decreases seeking for a variety of reinforcer types may be useful in the development of treatments for craving-related behavior, including diet recidivism.

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Fig. 1.

Mean active and inactive lever responses, saccharin deliveries, and photobeam breaks during the Training phase. Each bar represents a separate group of animals ($n = 15$ or 16 rats/group). Means $\pm$ SEMs are indicated on the figure.

Fig. 2. Mean active and inactive lever responses, cue presentations, and photobeam breaks during the Testing phase. Each bar represents a separate group of animals ($n = 15$ or 16 rats/group). Means $\pm$ SEMs are indicated on the figure. An asterisk indicates a significant difference between the groups.

Fig. 3. Active lever responding time courses in the Testing phase. The 60-min cue-reactivity test session was divided into 6 blocks of 10 min. Each data point indicates mean response rates (number of active lever responses per min) $\pm$ SEMs.

Fig. 4.

Mean response rates (number of active lever responses per min) as functions of cumulative number of cue presentations. Each data point represents the average of the cumulative number of cue presentations at the beginning of a 10-min block, and the average of the response rate of that 10-min block.

Table 1

Parameters of Eq. 1 and the percentage of the variance accounted for (r^2) when Eq. 1 was fitted to each subject. The order of subjects was based on r^2 . The r^2 in bold indicates when Eq. 1 described the within-session changes in responding to be more than significant ($p < 0.05$). The critical value for r^2 was 0.659.

SAL	1 μg						10 μg								
	Subjects	y-axis	x-axis	slope	r ²	Subjects	y-axis	x-axis	slope	r ²	Subjects	y-axis	x-axis	slope	r ²
C7		14.5	16.3	0.888	0.971	C9	9.1	7.0	1.291	0.998	E12	4.9	4.6	1.063	0.934
C18		9.9	18.2	0.544	0.877	D4	12.8	14.5	0.883	0.932	C19	16.9	21.7	0.779	0.902
C3		13.6	20.8	0.650	0.877	C22	14.1	18.6	0.756	0.913	D9	19.6	10.9	1.798	0.882
C6		23.3	29.3	0.796	0.844	C16	17.3	21.0	0.821	0.870	E2	25.4	18.8	1.347	0.840
C23		12.9	17.9	0.719	0.836	D22	32.1	25.1	1.275	0.846	D7	20.6	6.5	3.147	0.836
D12		22.2	38.1	0.582	0.796	D18	24.7	16.3	1.516	0.836	C4	13.2	10.6	1.244	0.835
D5		13.7	25.0	0.548	0.793	D23	13.9	15.1	0.919	0.802	D6	19.1	11.9	1.610	0.813
E5		20.4	25.2	0.809	0.671	D8	26.2	30.2	0.868	0.796	D21	9.9	11.2	0.888	0.801
E4		10.4	9.4	1.115	0.663	E8	12.3	12.3	1.000	0.784	D15	15.9	13.5	1.174	0.553
E11		10.0	11.2	0.897	0.619	C8	19.1	26.4	0.721	0.689	C5	11.0	21.7	0.506	0.471
C21		8.1	18.2	0.446	0.546	C2	10.6	29.2	0.361	0.630	C12	2.1	3.3	0.625	0.457
D3		11.1	24.9	0.448	0.536	C11	6.7	11.8	0.569	0.573	D17	4.1	9.7	0.423	0.405
D16		8.9	21.5	0.413	0.413	D19	12.1	14.4	0.841	0.550	C14	7.7	16.7	0.461	0.397
E7		15.0	32.6	0.459	0.308	E3	6.2	14.2	0.438	0.472	C15	7.7	25.4	0.305	0.322
C17		14.7	24.3	0.605	0.196	C20	5.5	90.1	0.061	0.009	C10	4.2	9.5	0.444	0.165
D24		11.0	55.5	0.199	0.182										