Published in final edited form as:
Behav Neurosci. 2009 December ; 123(6): 1279–1287. doi:10.1037/a0017702.

Dopamine D1 and D2 antagonist effects on Response Likelihood and Duration

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Abstract

Experimentally-induced and Parkinsonian disruptions in dopamine (DA) transmission are associated with motor abnormalities that include a reduced likelihood of behavioral response initiation and an increased duration of executed responses. Here we investigated the dopamine receptor subtypes involved in regulating these two aspects of behavior. We examined the effects of D1 family (D1/D5) antagonist R(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (SCH23390; 0, 0.04, 0.08 or 0.16 mg/kg) and D2/D3 antagonist 3,5-Dichloro-N-(1-ethylpyrrolidin-2-ylmethyl)-2-hydroxy-6-methoxybenzamide (+)-tartrate salt (raclopride; 0, 0.2, or 0.4 mg/kg) on the likelihood and duration of a cued Pavlovian approach and a cued operant lever-press response. While the high doses of the D1 and D2 antagonists produced similar levels of overall locomotor suppression, only the D2 antagonist increased the duration of time that animals' heads remained in the food compartment during both Pavlovian and operant task performance. In contrast, D1 antagonist SCH23390 decreased the proportion of trials in which animals executed both the Pavlovian approach and operant lever-press, while raclopride did not. The results suggest that D2 receptor blockade preferentially increases response duration, and, under the simple discrete-trial procedures employed here, D1 receptor blockade preferential reduces Pavlovian and operant response likelihood.

Keywords

SCH23390; raclopride; motor; initiation; rat

The expression of many unconditioned and learned behaviors can be disrupted by both D1 and D2 antagonist drugs. For instance, both D1 and D2 antagonists reduce locomotor activity (Baik *et al.*, 1995; Baldo, Sadeghian, Basso, & Kelley, 2002; Choi, Balsam, & Horvitz, 2005; Eyny & Horvitz, 2003) and rates of appetitively-motivated operant behavior (Beninger & Miller, 1998; Cousins, Wei, & Salamone, 1994; Domenger & Schwarting, 2006; S. C. Fowler & Liou,

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1998). However, at least one aspect of behavioral expression, the *duration* of behavioral acts, appears to be modulated relatively specifically by D2 (relative to D1) receptor antagonists. For instance, the duration of time between a head entry into and withdrawal from a food compartment is increased by systemically-administered D2 receptor antagonists (S. C. Fowler & Liou, 1994, 1998; Horvitz & Eyny, 2000), while D1 antagonists have little or no effect on the duration of individual head entries (S. C. Fowler & Liou, 1994, 1998). Similarly, the time between the press and release of an operant manipulandum is preferentially sensitive to the duration-increasing effects of D2 compared to D1 receptor blockade (S. C. Fowler & Liou, 1994).

We have previously observed that systemic D1 receptor blockade reduces the proportion of trials on which a conditioned stimulus (CS) elicits an approach response, an effect which we did not observe following D2 receptor blockade (Choi *et al.*, 2005). Other studies have similarly reported that cued response expression is disrupted by D1 (Nicola, Taha, Kim, & Fields, 2005; Yun, Nicola, & Fields, 2004) and not D2 (Hauber, Bohn, & Giertler, 2000; Yun *et al.*, 2004) receptor blockade, although in several studies of cued responding D2 antagonist-induced disruptions in response expression have been observed (Pattij, Janssen, Vanderschuren, Schoffelmeer, & van Gaalen, 2007; Smith, Smith, Zigmond, Amalric, & Koob, 2000; Wadenberg, Ericson, Magnusson, & Ahlenius, 1990).

In the current study, we examined the effects of selective D1 or D2 receptor antagonists on both response duration and response likelihood in a cued Pavlovian approach or a cued operant lever-press task in which a single behavioral response was tied to a single exteroceptive stimulus. We report that under these simple cued Pavlovian approach and operant lever press tasks, systemic D2 and not D1 receptor blockade increased the duration of head entries into the food compartment, while D1 and not D2 receptor blockade reduced the proportion of trials on which rats emitted a Pavlovian approach or an operant lever press.

Methods

Subjects

Male Sprague-Dawley rats (275-350 g) obtained from Charles River laboratories (Wilmington, MA) were housed in pairs within Plexiglas cages (22 cm high × 22 cm wide × 46 cm deep) mounted on a rack within an animal colony, with food and water freely available. The colony was maintained at approximately 23°C, with a 12-hr light-dark cycle (lights on at 8:00 A.M.). Rats were gently handled during their first week of arrival and placed on a 23-hr food deprivation schedule for the remainder of the experiments.

Apparatus

Behavioral sessions were conducted in eight chambers (29 cm high × 29 cm wide × 25 cm deep; Coulbourn Instruments, Allentown, PA) individually housed within sound- and light-attenuated enclosures. Two opposite walls of the chamber were Plexiglas; the other two were metal. A house light was located at the top center of one metal wall, 2 cm below the ceiling. Recessed within the bottom center of this wall, 2 cm above the floor, was a food compartment (4.0 cm high × 3.0 cm wide × 2.5 cm deep), into which food pellets (Bioserve F0021 45 mg, Frenchtown, NJ) were delivered. An infrared photo-emitter-detector was located on the sides of the food compartment, and interruption of the photobeam signaled to the computer (Dell Pentium) the presence of the animal's head within the food compartment. Added to the conditioning chambers in the cued lever-press experiment were 1) a speaker (Coulbourn, H12-01R), mounted on the left corner of the same wall, 4 cm below the ceiling, which generated the discriminative tone stimulus (1000 Hz, 68 dB) signaling the availability of food for the next lever-press, and 2) a lever (Coulbourn, E21-03), centered 10 cm to the left of the food

trough, 2.5 cm above the floor chamber, and actuated with a minimum of 25 g-equivalent weight. Locomotor counts, examined in the cued approach experiment, were assessed via an infrared activity monitor (Coulbourn H24-61) employing a differential detector to sense the animals' emitted infrared body heat image (13 nM infrared radiation) through an array of lens facets on two detector elements, with relative changes in the energy falling on the elements defined as movement unit. A PC running Coulbourn L2T2 or Graphic State software recorded the time of head entries and withdrawals, pellet deliveries, movement counts, tone presentations, locomotor counts and lever-presses with 50 ms resolution.

Drugs

R(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (SCH 23390; Sigma Chemical, St. Louis, MO), a highly selective antagonist of the D1 family (D1/D5) (Iorio, Barnett, Leitz, Houser, & Korduba, 1983; Missale, Nash, Robinson, Jaber, & Caron, 1998) or 3,5-Dichloro-N-(1-ethylpyrrolidin-2-ylmethyl)-2-hydroxy-6-methoxybenzamide (+)-tartrate salt (raclopride; Sigma Chemical), a highly selective antagonist of D2/D3 receptors (Missale *et al.*, 1998; Protais, Chagraoui, Arbaoui, & Mocaer, 1994) were dissolved in isotonic saline, and injected intraperitoneally in a volume of 1 ml/kg of body weight 30 min prior to test sessions.

Cued Approach

Several seconds after placement in the conditioning chamber, a house light was illuminated, and remained lit until the session ended. During each session, rats received 28 pellets (trials) delivered individually into the food compartment on a variable-time (VT) 70 s schedule with a minimum inter-trial interval (ITI) of 30 s. (At 20 sec intervals, a given ITI had a 0.33 probability of termination; an additional 10 sec constant was then added to each ITI). Activation of the food magazine produced a 400-ms 78-dB sound generated by the feeder motor which served as the CS. The pellet settled at the bottom of the food compartment approximately 600 ms after feeder activation. The times of each head entry into the food compartment, removal of the head from the compartment, and locomotor count were recorded for all sessions. At the end of each session, animals were returned to their home cages and provided with free food for one hour. Independent groups of rats were trained drug-free for 2 consecutive days and tested on the following day under the influence of one of the following drug doses: vehicle (n=8), 0.04 (n=8), 0.08 (n=8) or 0.16 mg/kg (n=8) of D1 antagonist SCH 23390 or vehicle (n=11), 0.2 (n=7), or 0.4 mg/kg (n=14) of D2 antagonist raclopride. The between-groups design, employed here and in the cued lever press experiment (below), to assess behavioral effects of drug dose has the advantage of avoiding drug sensitization effects that can confound repeated measures designs.

Cued Lever-press

This experiment was designed to mirror the test conditions of the cued approach paradigm above, but required an operant lever-press for reward delivery. Pre-training began with a single magazine training session in which the lever was absent from the chamber, and 28 pellets were delivered on a VT 70 s schedule. On the following day, the lever was placed into the chamber, and animals were permitted to lever-press under a continuous reinforcement (CRF) schedule for 20 minutes. Single daily CRF sessions continued until animals had pressed the lever at least 20 times on two consecutive days (requiring 2 to 4 training sessions; mean = 2.4 sessions).

Following CRF acquisition, animals received pre-training on the cued lever-press task. During these sessions, while the lever was continuously present, rats received 28 trials in which a 500 ms tone served as a discriminative stimulus (DS) that signaled the availability of food reward for the next lever-press. A lever-press triggered food pellet delivery only if it occurred within 10 s of tone onset. If animals failed to press the lever within 10 s of tone presentation, no food

was delivered during that trial. A VT 30 s ITI was employed until animals reached the performance criterion of earning a pellet on 20 of the 28 trials (1-5 sessions; mean = 1.9 sessions). Subsequent sessions employed a VT 50 s ITI until the same performance criterion was achieved (1-3 sessions, mean = 1.3 sessions), then a final VT 70 s ITI was instituted. After animals had reached the same performance criterion on the cued lever-press task with a VT 70 s ITI (1 session for all animals), they received two additional days of training under this experimental condition. On the following day, animals were pretreated with either vehicle (n=8), 0.08 (n=9), or 0.16 (n=7) mg/kg of D1 antagonist SCH23390, or vehicle (n=7), 0.2 (n=8) or 0.4 mg/kg (n=8) mg/kg of D2 antagonist raclopride.

Data analysis

For the *cued approach* experiment, the times of each head entry and head withdrawal from the food compartment were analyzed from 16 sec before (ITI sampling period) to 10 sec after each of the 28 cue presentations. For the *cued lever-press* experiment, the times of each head-entry and –withdrawal as well as the time of each lever-press and -release were analyzed from 16 sec before to 10 sec after each cue presentation. In the *cued approach* experiment, one animal in the 0.4 mg/kg raclopride condition, and two in the 0.16 mg/kg SCH23390 condition, emitted fewer than two head entries during the ITI baseline period and were therefore excluded from analysis of ITI (non-cued) head durations. In the *cued lever-press* experiment, two animals in the 0.16 mg/kg SCH group emitted fewer than two head entries during the ITI baseline period, and were also omitted from analysis of ITI head duration.

Trials for which rats failed to enter the food compartment within 10 s of CS presentation (*cued approach*) or to press the lever within 10 s of DS presentation (*cued lever-press*) were designated ‘missed trials’, and a latency score of 10 s was assigned. Drug effects on cued approach or cued lever-press latencies were first assessed by examining ‘total latencies’, with 10 s maximum scores for missed trials included. For groups showing drug-induced increases in total latency, follow-up analyses examined a) the proportion of trials that the animals ‘missed’, and b) ‘adjusted latency’, with missed trials excluded from the analysis. Locomotor behavior was examined across entire sessions during the Cued Approach task.

Results

Cued Approach

Figure 1 shows raster plots of head entries for representative animals performing the cued approach task under the influence of vehicle, SCH23390 or raclopride. The plots depict the time during which the rat's head was in the food compartment (horizontal lines) from 16 s before to 10 s after CS presentation. The 28 trials are stacked from bottom to top. As can be seen, SCH23390 (middle raster) reduced the likelihood of the rat's head entering the food compartment both in response to the CS and during ITIs, but did not affect the duration of individual head entries. In contrast, raclopride (bottom raster) increased the duration of the rat's individual head entries without reducing the likelihood of entering the food compartment.

Figure 2 shows group data depicting the mean probability that the head was inside the food compartment for animals performing the cued approach task in the SCH23390 (vehicle, 0.04, 0.08 or 0.16 mg/kg) and raclopride (vehicle, 0.2, 0.4 mg/kg) groups before and after CS presentation. Lower peaks seen in the top panel, just after CS presentation, reflect the reduced proportion of trials in which SCH-treated animals emitted a head entry response; wider peaks seen in the bottom panel represent increased duration of head entries in raclopride treated rats (see statistical analyses below).

The D1 antagonist SCH23390 increased the mean latency to enter the food compartment upon CS presentation ($F[3, 28]=8.37$, $p<0.0005$), while the D2 antagonist raclopride did not ($F[2, 29]=1.09$, p=n.s.). To better understand the nature of this SCH 23390-induced effect on response latency, a one-way ANOVA with missed trials excluded from the latency scores (i.e. analysis of 'adjusted latency') was conducted. Under this analysis, no effect of SCH23390 was observed, $F(3,31)=1.68$, p=n.s. Thus, for trials in which rats responded to the cue within 10 sec of CS presentation, SCH23390 did not affect the latency of the head entry response. This suggested that the effect of SCH23390 on overall latency to respond to the cue was due to an increased proportion of trials in which rats did not respond to the cue and received a 10 sec maximum score. Confirming this interpretation, a one -way ANOVA showed that SCH23390 significantly increased the proportion of trials missed, $F(3, 28)=9.42$, $p<0.0005$ (see figure 3). Thus, the likelihood of executing the cued approach was dependent upon D1, but not D2, receptor transmission. Further, D1 antagonist-induced deficits in executing the cued approach were due to a decreased likelihood of responding to the CS, rather than to a slowing of initiated responses.

Analysis of head entries during the baseline period 10 sec before CS presentation showed that SCH23390 reduced the frequency of head entries occurring during the ITI, $F(3, 28) = 29.89$, $p<0.0005$, while D2 antagonist raclopride did not, $F(2, 29) = 1.03$, p=n.s. D1 antagonist SCH23390 therefore reduced the likelihood of approaches to the food compartment both in response to the CS and during ITIs. Raclopride did not reduce the likelihood of approach to the food compartment either in response to the CS or during the ITI.

Analysis of the duration of individual head entries showed that D2 antagonist raclopride increased head entry durations (log transformed to correct for unequal variance between groups) both for the first head entry response after CS presentation, $F(2,29) = 13.25$, $p<0.0005$ and for those occurring during the ITI, $F(2,28)=10.92$, $p<0.005$. In contrast, D1 antagonist SCH23390 produced a moderate *reduction* in the duration of individual head entry responses to the CS, $F(3,28)=3.14$, $p<0.05$, and produced no effect on the duration of head entries emitted during ITIs $F(3,25)=1.16$, p=n.s. The fact that the D2 antagonist increased response durations both during the ITI and following the CS suggest that the duration-increasing effect of the drug is not due to an increased amount of time for animals to consume pellets.

Cued Lever Press

Analysis of D1 and D2 antagonist effects on response likelihood and duration in the cued lever-press task largely, although not entirely, mirrored those observed in the Pavlovian cued approach paradigm. D1 antagonist SCH23390 increased the latency to lever-press upon cue presentation, ($F [2, 21] = 11.56$, $p <0.0005$), while D2 antagonist raclopride did not ($F [2, 20] = 0.85$, p = n.s.). Follow-up analyses showed that SCH23390 both increased the 'adjusted latency' to lever-press upon cue presentation (with missed trials excluded from the analysis), $F[2,21]= 6.07$, $p<.01$, and increased the proportion of cued lever-press trials missed (figure 4), $F[2,21] = 10.34$, $p<.001$. Therefore, in both the Pavlovian approach and operant lever-press tasks, D1 and not D2 receptor blockade disrupted the initiation of cued goal-directed responses. While the disruptive effect of SCH23390 on the Pavlovian approach response was due to a reduction in the likelihood of responding to the cue and not to a slowing of initiated responses, in the cued lever-press task the D1 antagonist both reduced response likelihood and increased the latency of executed responses.

The frequency of lever-pressing during the ITI was also reduced by SCH23390, $F [2, 21] = 3.96$, $p < 0.05$, and not by raclopride, $F [2, 20] = 0.85$, p = n.s. D1 receptor blockade therefore reduced the likelihood of operant lever-press execution both under cued and non-cued conditions; D2 receptor blockade did not affect the likelihood of operant response execution under either cued or non-cued conditions.

The duration of individual lever-presses (again, log transformed to normalize group variance) was unaffected by either SCH23390 $F(2,20) = 0.96$, p=n.s., or raclopride $F(2,20) = 0.48$, p=n.s. However, some caution is appropriate in interpreting this negative effect. A previous study that reported a raclopride-induced increase in the duration of individual lever-presses (S. C. Fowler & Liou, 1994) employed an operant manipulandum requiring a lower force requirement for reinforcer delivery (8 g-equivalent weight compared to the current 25 g-equivalent weight) and higher time resolution (10 ms) of recordings compared to that employed here. In addition, their operant manipulandum was positioned in such a way as to restrict the body position of the animal as it engaged the manipulandum, thus restricting operant response topographies and, likely, reducing within-group and within-subject variance in observed durations of manipulandum contact. These methodological differences may account for the failure to observe D2 antagonist-induced increases in lever-press duration in the present study.

After rats pressed the lever, they were of course required to place their head into the food compartment in order to collect pellets, and occasionally entered the food compartment during ITIs. Raclopride increased the duration of head entries occurring during the ITI, $F(2,20) = 3.89$, $p<.05$, and produced a marginally significant increase in the duration of the first head entry following reward presentation, $F(2,20) = 3.20$, p=.06. In contrast, SCH23390 did not affect head entry durations during the ITI, $F(2,18) = 2.45$, p= n.s. or the duration of the head entry following reward presentation $F(2, 20) = 1.12$, p= n.s. In summary, D2 and not D1 receptor blockade increased the duration of individual head-entries into the food compartment both in the cued approach and the cued lever-press paradigms, while D1 and not D2 receptor blockade reduced the likelihood of the Pavlovian approach and the operant lever-press, both in response to the cue and during ITIs.

Locomotor behavior was reduced by SCH23390, $F(3, 28)=3.90$, $p<0.05$ and raclopride $F(2, 29)=11.44$, $p<0.0005$ (see figure 5). Rats under the influence of the high dose of SCH23390 and the high dose of raclopride showed comparable levels of locomotion. Because the vehicle control for the raclopride group was more active than the vehicle control for the SCH group, the percent suppression produced by the high dose of SCH (approximately 50%) is less than that produced by the high dose of raclopride (approximately 70%). Despite the fact that the high dose of SCH23390 produced an equal or lesser disruption in locomotor behavior than did the high dose of raclopride, SCH23390 reduced both Pavlovian and operant response likelihood, while raclopride did not. Taken together, while both D1 and D2 receptor blockade suppressed locomotion, D1 receptor blockade preferentially reduced the likelihood of Pavlovian and operant response execution while D2 receptor blockade preferentially increased the duration of individual head entries.

Discussion

At dose ranges for which D1 antagonist SCH23390 and D2 antagonist raclopride produced similar levels of locomotor suppression, SCH23390 reduced the probability of performing both a Pavlovian approach and an operant lever-press. D2 antagonist raclopride did not reduce the probability of performing either behavioral response. In contrast, raclopride increased the duration of head entries in the food compartment, while SCH23390 did not increase response duration.

While Pavlovian and operant response likelihood was reduced by D1 antagonist SCH23390, and not by D2 antagonist raclopride, it is possible that a higher raclopride dose may have reduced response likelihood as well. Although the highest dose of raclopride (0.4 mg/kg) produced locomotor suppression to an extent that was at least as large as that produced by the highest SCH23390 dose, it is possible that the raclopride dose required to suppress locomotion may be less than that required to disrupt response initiation. Nevertheless, at doses of raclopride

that were sufficient to strongly suppress locomotion and to lengthen the duration of head entry responses, the D2 antagonist did not reduce the probability of performing either a Pavlovian head entry or an operant lever press under either cued or non-cued conditions. This pharmacologically-specific effect of D1 receptor blockade on response likelihood is consistent with previous work showing that the likelihood of executing a cued operant nose-poke or lever-press for food reward is reduced by intra-accumbens D1 (Nicola *et al.*, 2005; Yun *et al.*, 2004) and not by D2 receptor blockade (Hauber *et al.*, 2000; Yun *et al.*, 2004). However, as described below, a number of studies have observed D2 antagonist-induced disruption of response initiation.

Both D1 and D2 receptor transmission may contribute to a number of processes relevant to behavioral expression, including the energizing (Berridge & Robinson, 1998; Salamone & Correa, 2002; Salamone, Cousins, & Snyder, 1997), and selection (Horvitz, 2002; Humphries, Stewart, & Gurney, 2006) of behavioral responses. Therefore in order for *D1 antagonist-specific* response initiation deficits to be observed, several 'boundary conditions' may be necessary. In studies employing a larger number of trials per session than that employed here, D2 antagonists produce within-session reductions in appetitive operant responding (Fouriezos & Wise, 1976; S.C. Fowler, 1990) at raclopride doses within the range employed here (Domenger & Schwarting, 2006; MacDonald & Meck, 2006). In these cases, while D2 antagonists reduced the rate (i.e., the probability per unit time) of responding, they did so under conditions where maintenance of high response rates were necessary in order for drugged animals to perform comparably to vehicle controls. D2 antagonist-induced decrements in response rate are particularly pronounced under high ratio schedules that require sustained responding for reinforcer delivery (Domenger & Schwarting, 2006; Salamone *et al.*, 1997). It is therefore possible that D2 receptor blockade reduces response likelihood when response-maintenance requirements are high. In the current tasks, response maintenance requirements were relatively low, for drug effects were examined during a single session involving 28 presentations of an eliciting stimulus that occasioned a single Pavlovian or operant behavioral response.

D2 antagonists also disrupt response initiation under cued response paradigms that involve multiple behavioral response alternatives (Domenger & Schwarting, 2006; Pattij *et al.*, 2007). In the present tasks, animals performed a single behavioral response to a single Pavlovian or operant sensory cue. It is possible that D1-specific effects on response likelihood are most clearly observed with simple cued response paradigms that do not require subjects to choose among behavioral response alternatives or to sustain high levels of behavioral responding.

We found that the duration of head entry into the food compartment was lengthened by D2 antagonist raclopride and not by D1 antagonist SCH23390 in both the Pavlovian approach and operant lever-press tasks. This was observed for head entries occurring in response to the Pavlovian cue, following a reinforced lever-press (i.e., when the food compartment contained a food pellet) and also for head entries occurring during ITIs (when the food compartment was empty). The latter finding rules out increased food consumption time as a likely explanation for this D2 antagonist-induced increase in head entry duration. These results are consistent with previous studies showing that D2 antagonists increase the duration of time between head entry and withdrawal from a food compartment (S. C. Fowler & Liou, 1994, 1998; Horvitz & Eyny, 2000) and, with the amount of time that the forepaw is in contact with an operant manipulandum (S. C. Fowler & Liou, 1994). As noted in the Results section above, we did not observe the latter effect here, likely due to methodological factors.

Consistent with the observation that reduced transmission at D2 receptors causes a lengthening of motor response components, D2 antagonists appear to increase the duration of non-resting

body postures. For instance, D2 antagonists can increase freezing behavior (Blackburn & Phillips, 1990) and muscle rigidity (Hemsley & Crocker, 2002; Wu, Hyland, & Chen, 2007), and at high doses can cause catalepsy (Boulay *et al*., 2000). Muscle rigidity and catalepsy are both associated with D2 receptor blockade within dorsal-anterior regions of the striatum (Ellenbroek, Schwarz, Sontag, Jaspers, & Cools, 1985). Interestingly, however, catalepsy can be induced by D2 or D1 receptor blockade (Hauber, Neuscheler, Nagel, & Muller, 2001; Wanibuchi & Usuda, 1990; Zarrindast & Habibi-Moini, 1991). The framework proposed here suggests the possibility that D1 and D2 antagonist-induced catalepsy may be caused by different mechanisms: the former by a failure to initiate a command for the upcoming motor act, and the latter by a prolongation of the current body position due to muscle rigidity.

While DA antagonist-induced increases in response duration could be secondary to a failure to initiate a subsequent motor command, the reverse is also possible, i.e., that D2 antagonist-induced reductions deficits in response initiation may in some cases be secondary to increases in the duration of measured or unmeasured behavioral acts, e.g., the prolonged duration of a particular body posture that precedes a measured behavioral act. It is possible, for instance, that the D2 antagonist-induced impairment in response initiation in paradigms in which a lever-press response is initiated *prior to* the movement trigger cue that elicits a lever-withdrawal response (Amalric, Berhow, Polis, & Koob, 1993) is secondary to the increased duration of the animal's lever-press posture at the time that the ‘withdrawal’ trigger cue is presented.

Interestingly, involvement of D1 and D2 receptor transmission in modulating response likelihood and duration, respectively, corresponds to what might be predicted on the basis of their anatomical localization within basal ganglia circuitry. D1 receptors are predominantly expressed in striatal neurons comprising “direct” basal ganglia pathways, while D2 receptor density is greatest in “indirect” pathway neurons (Deng, Lei, & Reiner, 2006; Gerfen, Keefe, & Gauda, 1995; Le Moine & Bloch, 1995; Wichmann & DeLong, 1996). Via the direct pathway, cortically-initiated movements signals to the striatum lead to increased thalamocortical drive. Direct pathway activity has been postulated to serve a movement-gating function, promoting the expression of cortically-initiated movement signals (Alexander & Crutcher, 1990; DeLong, 1990). Such models of basal ganglia function further postulate that indirect pathway activity is associated with decreased thalamocortical drive, and serves as a ‘brake’ on these movements signals. If so, D1 receptors would be expected to modulate the likelihood of response initiation while D2 receptors would be expected to modulate the disengagement (i.e., duration) of behavioral responses. The present results are consistent with this view. Of course, the direct/indirect pathway model above is only one of several which might account for the apparent preferential roles of D1 and D2 receptors in response likelihood and duration. D1 receptors, for instance, may contribute importantly to behavioral response engagement via actions within the prefrontal cortex (Hauber, 1998) and ventral striatum (Nicola et al., 2005; Yun et al., 2004), possibly related to maintenance of representations of the to-be-initiated behavior or the desired reward outcome (Horvitz, 2009). A key aim of future work should be to reveal the central sites mediating dissociable effects of D1 and D2 receptor blockade on response likelihood and duration, respectively.

Acknowledgments

This work was supported by NIDA grant DA023641.

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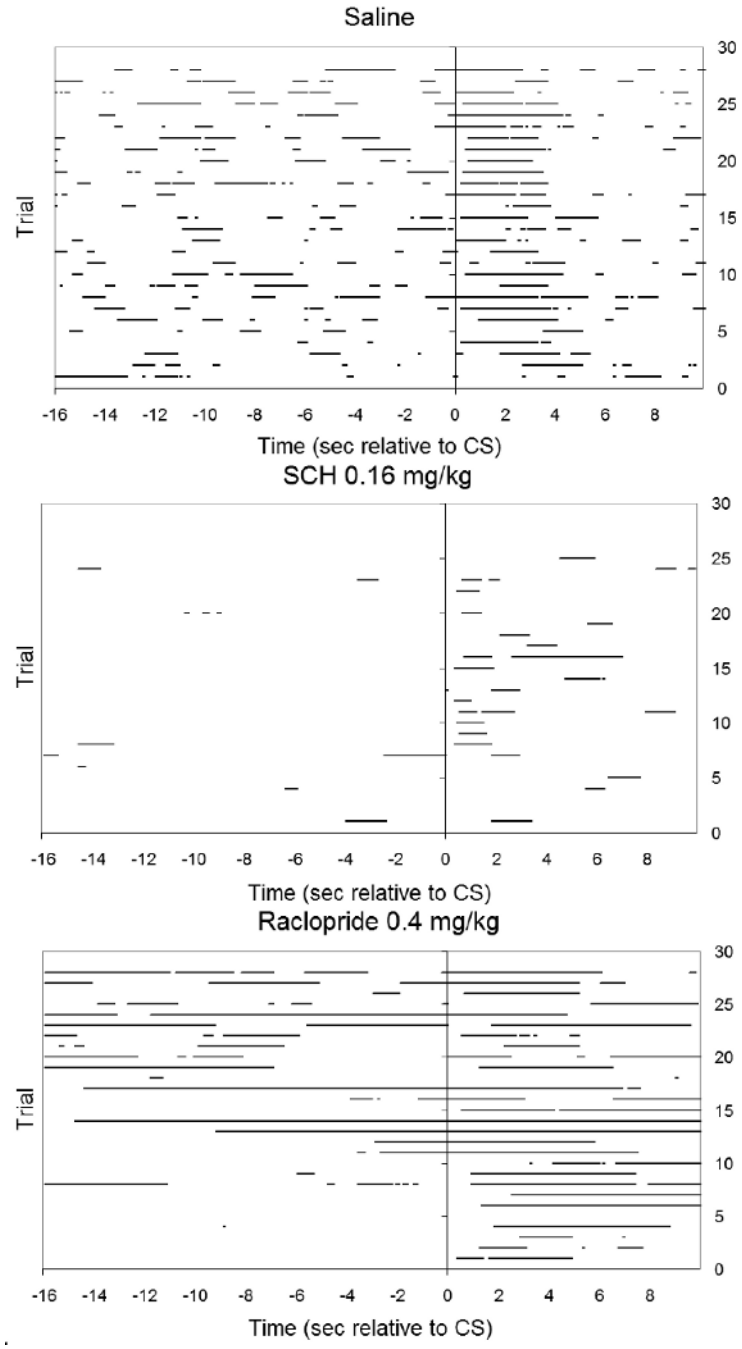

Figure 1.

Raster plots of individual head entries (horizontal lines) over the 28 trials (rows from bottom to top of y-axis) of the test session for representative animals performing the cued approach task under the influence of vehicle (top), D1 antagonist SCH23390 (middle) or D2 antagonist raclopride (bottom). D1 receptor blockade reduced the likelihood of head entries to the food compartment without affecting the duration of individual head entries. In contrast, D2 receptor blockade had little effect on head entry likelihood, but increased the duration of individual head entries.

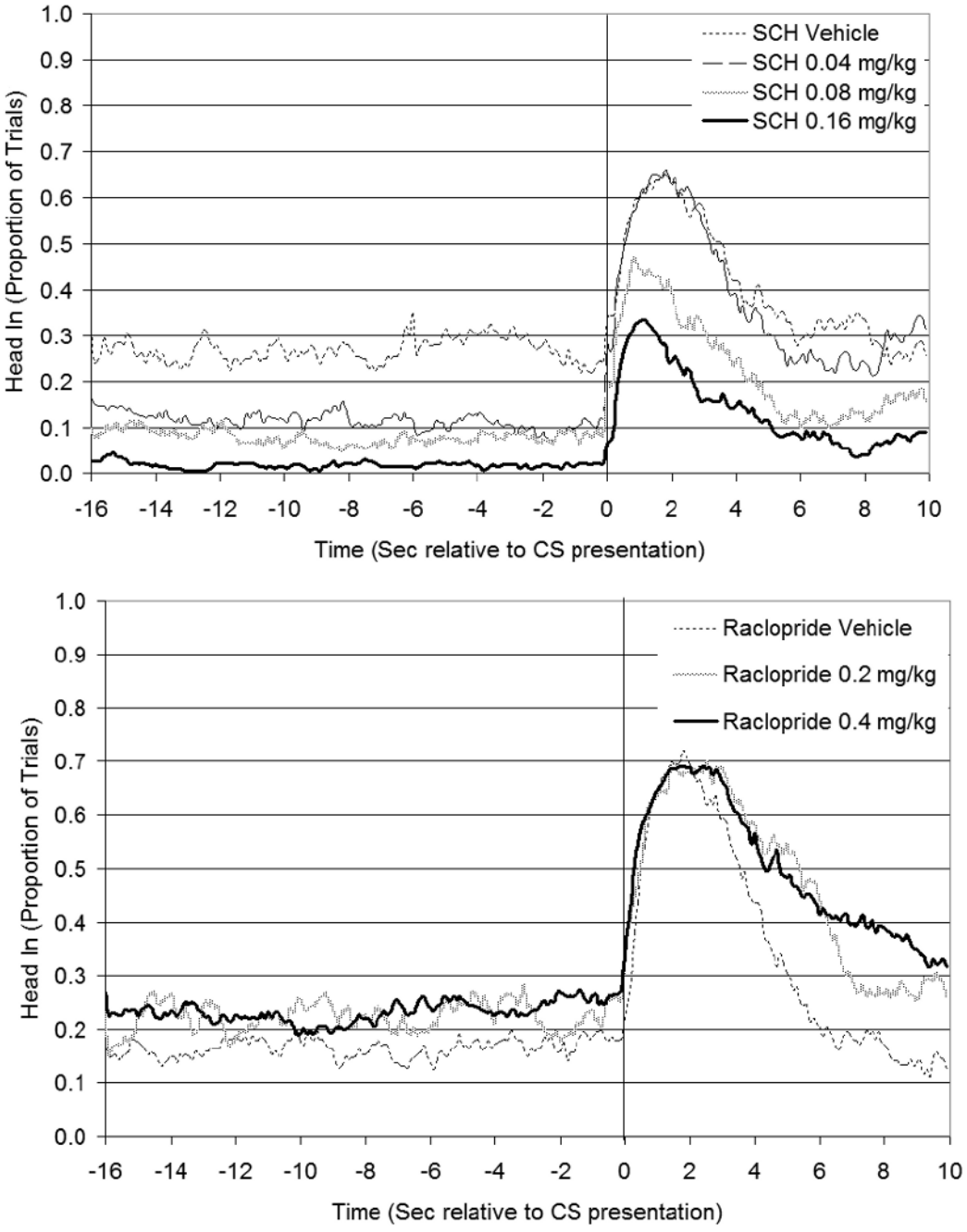

Figure 2.

Probability of the animal's head being inside the food compartment (y-axis) for each successive 100 ms bin during the 16 s before CS onset (-16 to 0), and the 10 s after the 500 ms CS in the cued approach task. D1 antagonist SCH23390 (top) did not increase head entry duration, but reduced the proportion of trials for which the animal responded to the CS, as reflected in the lower peaks after CS presentation. D2 antagonist raclopride (bottom) increased the duration of individual head entries without impairing initiation to the CS.

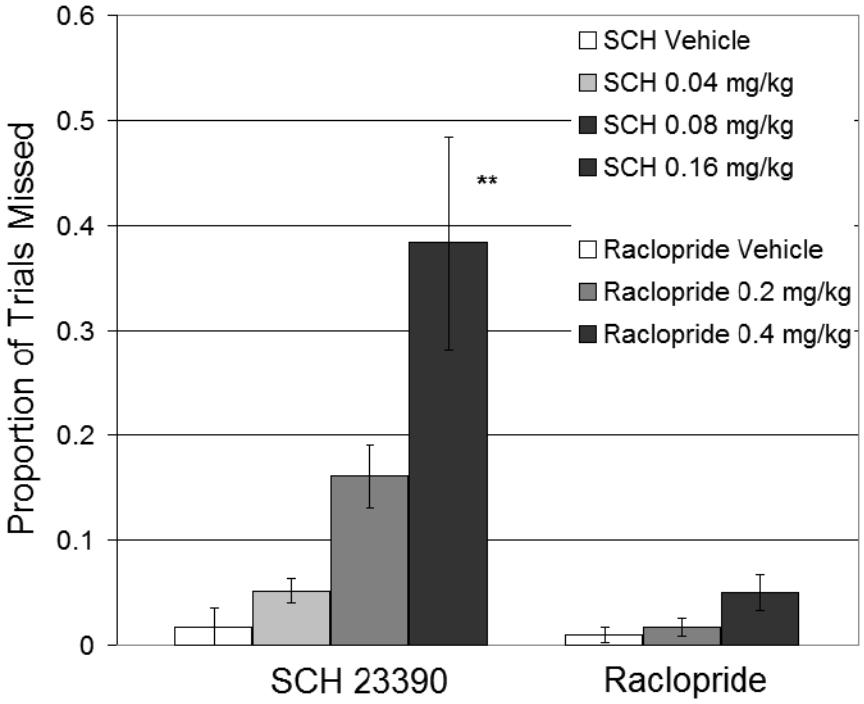

Figure 3.

Mean ± SEM proportion of the 28 Cued Approach trials missed (i.e., with response latency of > 10 s). D1 receptor blockade (left) significantly increased the proportion of trials for which animals failed to respond to the CS, while D2 receptor blockade (right) did not. Dunnett's comparison to vehicle control p<.001**

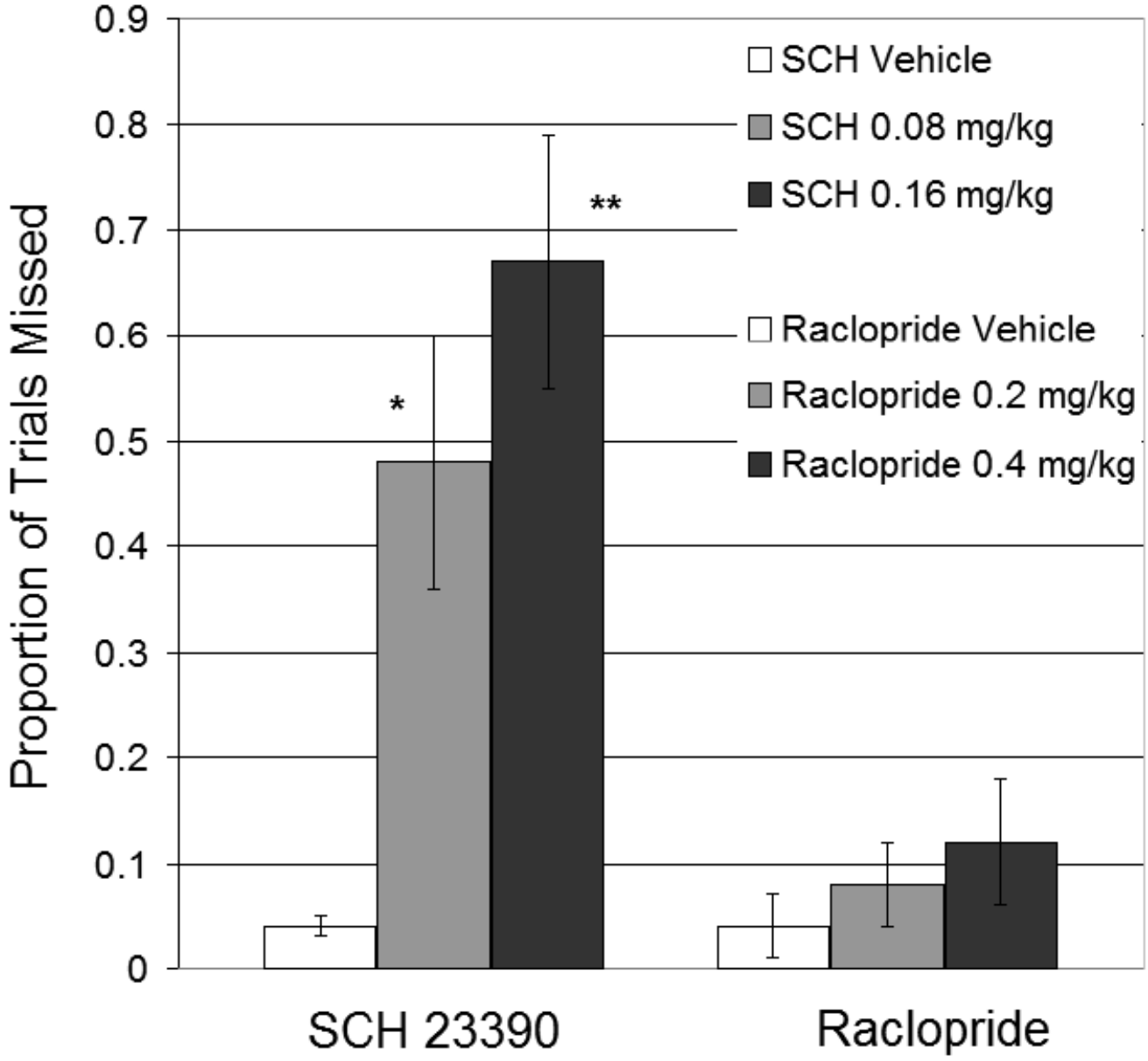

Figure 4.

Mean ± SEM proportion of the 28 Cued Lever-press trials missed (i.e., with response latency of > 10 s). D1 receptor blockade (left) significantly increased the proportion of trials for which animals failed to respond to the cue, while D2 receptor blockade (right) did not. Dunnett's comparison to vehicle control, p<.01*; p<.001**

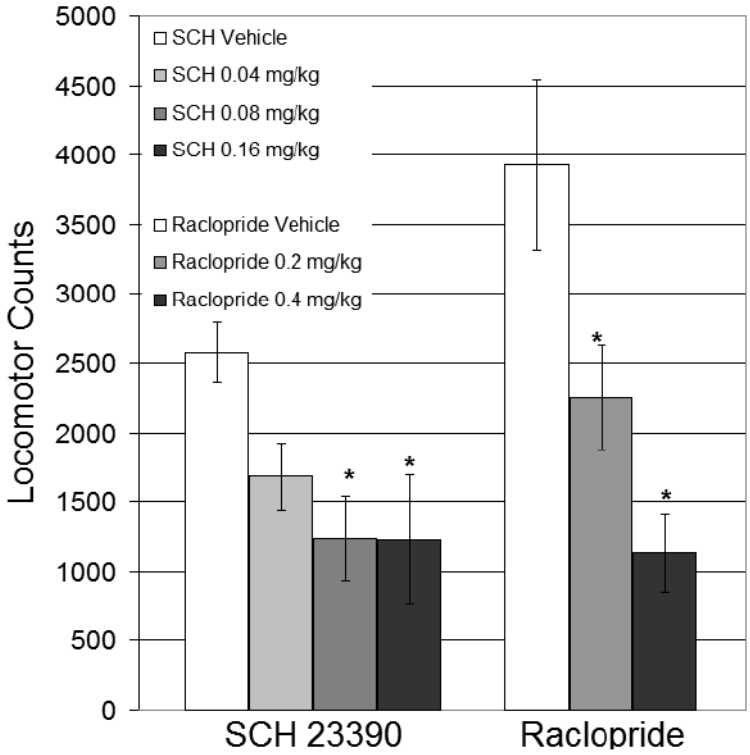

Figure 5.

Locomotor counts for animals under the influence of 0, 0.04, 0.08, or 0.16 mg/kg of D1 antagonist SCH23390 (left) or 0, 0.2, or 0.4 mg/kg of D2 antagonist raclopride (right) assessed in rats performing the cued approach task. Dunnett's comparison to vehicle control, $p<.05$ *.