Pharmacology, Biochemistry and Behavior 96 (2010) 40–47

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Disruption of conditioned reward association by typical and atypical antipsychotics

C.L. Danna *, G.I. Elmer

University of Maryland School of Medicine, Department of Psychiatry, Maryland Psychiatric Research Center, Maple and Locust Street, Baltimore, MD 21228, United States

ARTICLE INFO

Article history:
Received 8 April 2009
Received in revised form 31 March 2010
Accepted 7 April 2010
Available online 21 April 2010

Keywords:
Antipsychotic
Autoshape
Olanzapine
Haloperidol
Incentive salience
Goal-tracking
Sign-tracking

ABSTRACT

Antipsychotic drugs are broadly classified into typical and atypical compounds; they vary in their pharmacological profile however a common component is their antagonist effects at the D2 dopamine receptors (DRD2). Unfortunately, diminished DRD2 activation is generally thought to be associated with the severity of neuroleptic-induced anhedonia. The purpose of this study was to determine the effect of the atypical antipsychotic olanzapine and typical antipsychotic haloperidol in a paradigm that reflects the learned transfer of incentive motivational properties to previously neutral stimuli, namely autoshaping. In order to provide a dosing comparison to a therapeutically relevant endpoint, both drugs were tested against amphetamine-induced disruption of prepulse inhibition as well. In the autoshaping task, rats were exposed to repeated pairings of stimuli that were differentially predictive of reward delivery. Conditioned approach to the reward-predictive cue (sign-tracking) and to the reward (goal-tracking) increased during repeated pairings in the vehicle treated rats. Haloperidol and olanzapine completely abolished this behavior at relatively low doses (100 μg/kg). This same dose was the threshold dose for each drug to antagonize the sensorimotor gating deficits produced by amphetamine. At lower doses (3–30 μg/kg) both drugs produced a dose-dependent decrease in conditioned approach to the reward-predictive cue. There was no difference between drugs at this dose range which indicates that olanzapine disrupts autoshaping at a significantly lower proposed DRD2 receptor occupancy. Interestingly, neither drug disrupted conditioned approach to the reward at the same dose range that disrupted conditioned approach to the reward-predictive cue. Thus, haloperidol and olanzapine, at doses well below what is considered therapeutically relevant, disrupts the attribution of incentive motivational value to previously neutral cues. Drug effects on this dimension of reward processing are an important consideration in the development of future pharmacological treatments for schizophrenia.

© 2010 Elsevier Inc. All rights reserved.

1. Introduction

Repeated associations between a reward and neutral environmental stimuli gradually confer incentive motivational salience to the stimuli. The conferred motivational value endows the stimulus with the capacity to initiate goal-directed behavior and, under some conditions, support behavior leading to their presentation (Rescorla and Solomon, 1967). Environmental stimuli with conferred motivational salience and the internal drive state, act in concert to strengthen goal-directed behavior. The interplay between conditioned stimuli and internal drive plays a vital role in the pursuit of natural rewards. Disruptions in incentive salience attribution may play a role in numerous psychiatric conditions, such as the aberrant pursuit of ultimately debilitating goals (drug abuse, Everitt et al., 2001; Robbins and Everitt, 2002; Tomie et al., 2008) and the errant assignment of salience to environmental stimuli and internal representations (psychosis, Kapur, 2003; Roiser et al., 2009). Conversely, failed or dampened incentive salience attribution may contribute to avolition and result in the failure to pursue goals important to the quality of life.

Quantifying incentive salience is important for assessing potential disruptions in incentive motivation. To this end, the autoshaping paradigm provides a valuable means to quantify the degree to which environmental stimuli have acquired incentive motivational properties. In the autoshaping paradigm, repeated presentation of a stimulus (CS+) prior to the presentation of a reward (US) results in a conditioned response characterized by approach to and in some cases consumatory movements directed at the previously neutral cue (Brown and Jenkins, 1968; Gamzu and Williams, 1973). The process is critically dependent upon the information the conditioned stimuli convey about reward delivery and is therefore considered a Pavlovian process (Balsam et al., 2006; Schwartz and Gamzu, 1977). A unique and valuable aspect of autoshaping is the quantifiable progressive increase in conditioned approach toward the stimuli as it is increasingly endowed with incentive salience and the positive relationship between the magnitude of the reward and conditioned approach to the reward-predictive cue (Brown and Jenkins, 1968; Pellegrini et al., 2008). In this regard, autoshaping provides a valuable

* Corresponding author. Tel.: +1 410 402 6105; fax: +1 410 402 6066.
E-mail address: cstam003@umaryland.edu (C.L. Danna).

0091-3057/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2010.04.004

means to quantify the degree to which a cue has acquired incentive motivational properties.

Autoshaping depends in large part upon the integrity of the mesolimbic dopamine system and relies on the anterior cingulate, nucleus accumbens core and central nucleus of the amygdala (Robbins and Everitt, 2002). Interestingly, autoshaping only partially overlaps the circuit involved in an instrumental response that results in the presentation of a stimulus previously paired with reward (conditioned reinforcer). Potentiation of instrumental responding for a conditioned reinforcer is abolished following lesions of the nucleus accumbens shell (versus core) and basolateral amygdala (versus central nucleus) (Parkinson et al., 1999) whereas autoshaping is altered by lesions of the nucleus accumbens core and central nucleus of the amygdala (Parkinson et al., 2000). Dopamine plays a major role in the attribution and maintenance of incentive salience characterized in the autoshaping paradigm; conditioned approach is associated with dopamine release in the nucleus accumbens (Day et al., 2007; Tomie et al., 2000) and altered by dopamine antagonists and dopamine depletion (Dalley et al., 2002; Di Ciano et al., 2001; Parkinson et al., 2002; Phillips et al., 1981). However, in addition to the role of dopamine, recent studies have shown that AMPA, glutamate, norepinephrine, corticosterone and serotonin may also play a significant role in autoshaping (Di Ciano et al., 2001; Tomie et al., 2000) although they may be uniquely associated with different components of the process (Di Ciano et al., 2001) and involve different brain regions (Tomie et al., 2000). Clinically, the importance of dopamine's role in autoshaping and incentive salience is very relevant in conditions that are treated with dopamine antagonists, such as schizophrenia. The aforementioned differences in the neurobiological and neurochemical underpinnings of different aspects of reward processing open the possibility for differences in the consequences of widely used antipsychotics. It is possible that different aspects of reward processing may be more or less sensitive to antipsychotics with varied pharmacological profiles.

Antipsychotic drugs are generally classified into two broad categories. Typical, or first generation, antipsychotics act predominantly through the D2 dopamine receptors (DRD2), with relatively low affinity for other receptors (Seeman and Van Tol, 1994). Atypical, or second generation, antipsychotics have significant affinity for the DRD2 receptor, but also have significant affinities to other DA, serotonin, muscarinic and histamine receptors and vary in their rate of dissociation from the DRD2 receptor (Bymaster et al., 1996; Kapur and Seeman, 2000; Morimoto et al., 2002; Seeman and Van Tol, 1994). It is thought that the therapeutic efficacy of both classes against the positive symptom domain is primarily due to their interaction with the DRD2 (Kapur et al., 2000). Unfortunately, preclinical studies have shown that blockade or elimination of the DRD2 significantly diminishes the capacity to process rewarding events (Elmer et al., 2005; Phillips et al., 1981; Wise, 2008). In fact, the DRD2 antagonist properties of antipsychotics is hypothesized to be the primary mechanism responsible for neuroleptic-induced dysphoria that contributes to treatment non-compliance and diminished quality of life in patients with schizophrenia and other mental disorders treated with antipsychotics (Awad and Voruganti, 2004; King et al., 1995; Lewander, 1994; Mizrahi et al., 2007; Voruganti et al., 2000). The pharmacological profile of second generation antipsychotics may be less disruptive to phasic dopamine transmission. In this regard, clinical studies suggest that olanzapine may not disrupt attribution of incentive salience to a cue paired with reward as severely as haloperidol (Juckel et al., 2006a; Schlagenhauf et al., 2008). However, a recent study demonstrates a significant relationship between DRD2 occupancy and the negative subjective effects of olanzapine suggesting that dosing, as always, is an important consideration. A better understanding of how one of the most widely used atypical antipsychotic, olanzapine (Hermann et al., 2002), affects reward processing will improve our understanding of which deficits are a result of disease and which are a byproduct of pharmacological treatment.

Overall, two areas of interest are addressed in this study. First, the main purpose of the experiments described in this report is to evaluate the effects of haloperidol (HAL) and olanzapine (OLAN) on reward processing in a behavioral model designed to assess the induction of incentive motivational value to reward-predictive stimuli, namely autoshaping. Surprisingly no studies to our knowledge have utilized this paradigm to study the effects of antipsychotics. Second, as mentioned previously, appropriate dosing is essential to interpreting outcomes in antipsychotic medications studies (Kapur et al., 2003). In order to provide a dosing comparison (therapeutic index) for the two drugs utilized in our study, the effects of haloperidol and olanzapine on a schizophrenia based, therapeutically relevant behavioral endpoint, amphetamine-induced disruption of prepulse inhibition, was investigated as well. The diverse pharmacology and effects of the antipsychotics used in this experiment combined with unique perspective into reward processing that autoshaping affords may provide insight into neuroleptic-induced dysphoria that occurs at therapeutically relevant doses.

2. Methods

2.1. Animals

Adult (60–120 days old), male Sprague–Dawley rats (Charles River Laboratories) weighing approximately 250–350 g at the start of the experiment were used. Rats (1 per cage for autoshaping or 3 per cage for PPI) were provided unrestricted access to food and water until the start of the experiments. All experiments were conducted in strict accordance with the principals outlined in the NIH Guide for Care and Use of Laboratory Animals.

2.2. Apparatus

Six rat operant chambers (MedAssociates) were used. Each chamber was equipped with the following: A) Two custom built lights made of a translucent 6×6 cm panel lit from behind with white light. One light in each chamber was covered with translucent blue plastic to further emphasize the difference between the lights. The stimulus lights are placed one on either side of the pellet delivery system. B) A retractable lever. C) A pellet system that delivers a single 45 mg sucrose pellet in a small recessed receptacle. D) An infrared photo beam system to detect entrances into the recessed cubicle where the reinforcer is delivered and two vertically oriented photobeams in front of the cue lights to detect approaches to the cue light. The equipment was controlled using MedAssociates software (St. Albans, Vermont).

2.3. Behavioral assays

2.3.1. Autoshaping

Subjects were maintained at 85% of their free feeding weight. Rats were placed in the operant chamber for a session consisting of 30 trials. Each trial consists of a single CS+ or CS− presentation. Between each trial a retractable lever is presented and the animal is required to go to the opposite side of the box to press it in order to continue to the next part of the trial. As stated by Parkinson et al. (2000) this requirement ensures the animal is equi-distant from both stimuli at the time of presentation. This allows for more reliable calculation of approaches by minimizing chance approaches.

CS+ trial: The CS+ cue is illuminated for a variable interval of 20 s (±10 s). Immediately following CS+ termination a sucrose pellet is delivered into the receptacle. *CS−trial*: The CS− cue is illuminated for a variable interval of 20 s (±10 s). No pellet is delivered following cue termination. Thirty sec later the retractable lever is presented. CS+ and

CS− trials were presented pseudo-randomly. During the session approach behavior to the reinforcer (sucrose pellet) and cue lights are quantified by photobeam breaks. The subjects were trained for 9 days in the autoshaping paradigm.

Approach to the CS+ cue during its presentation is a conditioned response, sign-tracking, that reflects the transfer of incentive motivational value to the reward-predictive cue. Approach to the pellet dispenser during the CS+ presentation is a conditioned response, goal-tracking, that reflects the conditioned response anticipating reward delivery. Approach to CS− is a conditioned response-like performance that is not based on CS–US pairings and provides an estimate of pseudoconditioning of sign-tracking. Similarly, approach to the food trough during CS− is a goal-tracking conditioned response-like performance that is not based on CS–US pairings and provides an estimate of pseudoconditioning of goal-tracking.

2.3.2. Drug administration

Prior to each autoshaping session either, vehicle, haloperidol, or olanzapine (Sigma-Aldrich, St. Louis, MO) was administered to the subject. The subject was administered the same drug at the same dose each day of the experiment. Vehicle (haloperidol: dH2O, acetic acid, and NaHCO3; olanzapine: dH2O, glacial acetic acid, and 2 N NaOH) or one of four doses of the first generation antipsychotic haloperidol (3, 10, 30 or 100 μg/kg, i.p.) or one of four doses of the second generation antipsychotic olanzapine (3, 10, or 30 or 100 μg/kg, i.p.) was given each day during the autoshaping stage of the experiment. The injection volume for all injections is 0.1 ml/g body weight.

2.3.3. Statistical analysis

The number of approaches to both the CS+ and CS− lights while they were illuminated, the percent of trials in which the subject first approached the CS+ following stimulus presentation and the difference score (approaches during CS+ minus approaches during CS−) were used as the dependent variables. The number of beam breaks within the pellet dispenser during CS+, CS− and UCS presentation was also collected. The dependent variables were analyzed using a two-way repeated measures analysis of variance (ANOVA) (drug dose × trial). Drug comparisons were made using a three-way repeated measures ANOVA (drug × drug dose × trial). The cumulative number of pellet dispenser beam breaks during CS+ and CS− cue presentation was analyzed in a similar manner. All statistics were run using JMP software (Cary, NC).

2.4. Prepulse inhibition (PPI)

2.4.1. Apparatus

Startle response was monitored using SR Lab Startle Response System chambers (San Diego, CA). The system consisted of a startle chamber house in an isolation cabinet (28.8 cm W × 30.7 cm L × 28.5 cm H) equipped with an internal fan and light. A cylindrical (4 cm × 13 cm) holding apparatus of transparent acrylic resting on a four-pegged platform within the isolation chamber was used to hold each subject throughout the testing session. Each holding apparatus was equipped with a piezo-electric accelerometer below each platform to detect motion. Background noise and acoustic stimuli, controlled via the SR Lab microcomputer and interface assembly, were delivered through a speaker mounted in the ceiling of the isolation chamber. All test chambers were located in a sound attenuated experiment room (2.5 m × 2.8 m), which along with the individual isolation cabinets served to minimize external noise.

2.4.2. PPI protocol

Subjects were brought to a holding room at least 30 min prior to testing for habituation purposes. Saline, haloperidol or olanzapine was given 15 min prior to saline or amphetamine (Sigma-Aldrich, St. Louis, MO; 5.0 mg/kg, i.p.). Following the appropriate pretreatment condition each subject was placed in the holding cylinder with the isolation chamber. Subjects from all experimental conditions were tested in a counter-balanced manner ensuring that subjects from each condition were tested in each chamber and were equally distributed throughout the test period. Background noise (65 dB) was present throughout the test session. After a 5 min acclimation period each subject was presented with a series of 66 acoustic stimuli trials. The trials were presented in pseudorandom order. Five individual startles at 120 dB above background for 40 ms were given after the 10 min acclimation period and at the end of the session. During the 10 min test session, prepulse inhibition trials consisted of a single prepulse stimulus presented at 1, 3, 6, 12 or 15 dB above background for a 20 ms duration followed 100 ms later by presentation of the startle stimulus delivered at 120 dB for 40 ms. In total, 11 individual startle trials and 11 each of the 1, 3, 6, 12, or 15 dB prepulse inhibition trials were presented. Individual startle trials were presented consecutively in groups of four at the start and end of each session, as well as three additional times throughout the session. The remaining prepulse inhibition trials were presented in pseudorandom order throughout the session. A variable 11–15 s inter-trial interval was utilized. Each session lasted a total of 20 min. Holding chambers were cleaned with 75% ethanol solution between each test session.

2.4.3. Statistical analysis

Throughout the session, a series of trials was presented in which the subject was presented two stimuli; a weak prepulse stimulus of varying intensity followed by a 120 dB startle stimulus. These trials provide a means in which to assess sensorimotor gating. The ability of the preceding stimulus to attenuate the startle response to the 120 dB stimulus was analyzed by normalizing startle amplitude to the 120 dB stimulus. PPI is then analyzed as the percent decrease in startle amplitude as a function of the magnitude of the prepulse stimulus. A two-way repeated measures ANOVA (drug × prepulse intensity as repeated measure) was used to analyze the disruptive effects of amphetamine and the ability of antipsychotics to ameliorate those effects.

3. Results

3.1. Haloperidol

The effect of haloperidol administration (vehicle, 3, 10 and 30 μg/kg) on acquisition of an autoshaping task is shown in Fig. 1A,C,E. Subjects administered the 100 μg/kg dose of haloperidol did not approach either of the cues and made minimal investigation of the pellet dispenser. As a result of the impairment, this dose was excluded from all subsequent statistical analysis and is not plotted in the graphs.

3.1.1. Conditioned approach to CS

Repeatedly presenting the CS+ cue prior to reward delivery results in a gradual increase in approach to the reward-predictive cue. This was evidenced by the percent of trials in which the CS+ cue was first approached (Fig. 1A) (F(Trial) = 7.61; df = 2, 29, p<0.002) and the total number of approaches to the CS+ cue across trials (Fig. 1C; F(Trial) = 7.72; df = 2, 29, p<0.002). Haloperidol significantly disrupts the formation of this association and the approach to the reward-relevant cue in a dose-dependent manner (F(Dose) = 3.42; df = 3, 30, p<0.030). The CS+ cue gained incentive value during the training period in the 3 and 10 μg/kg treated subjects as evidenced by a gradual increase in approach to this cue. In contrast, the CS− cue was equally salient as the CS+ cue in the subjects treated with 30 μg/kg, indicating no meaningful association of the reward-predictive cue with reward delivery. Thus, as the dose is increased there is a slight but non-significant reduction in CS+ incentive value at the 3 and 10 μg/kg dose, then elimination of cue incentive value without altering the motivation or capacity to initiate each trial (task

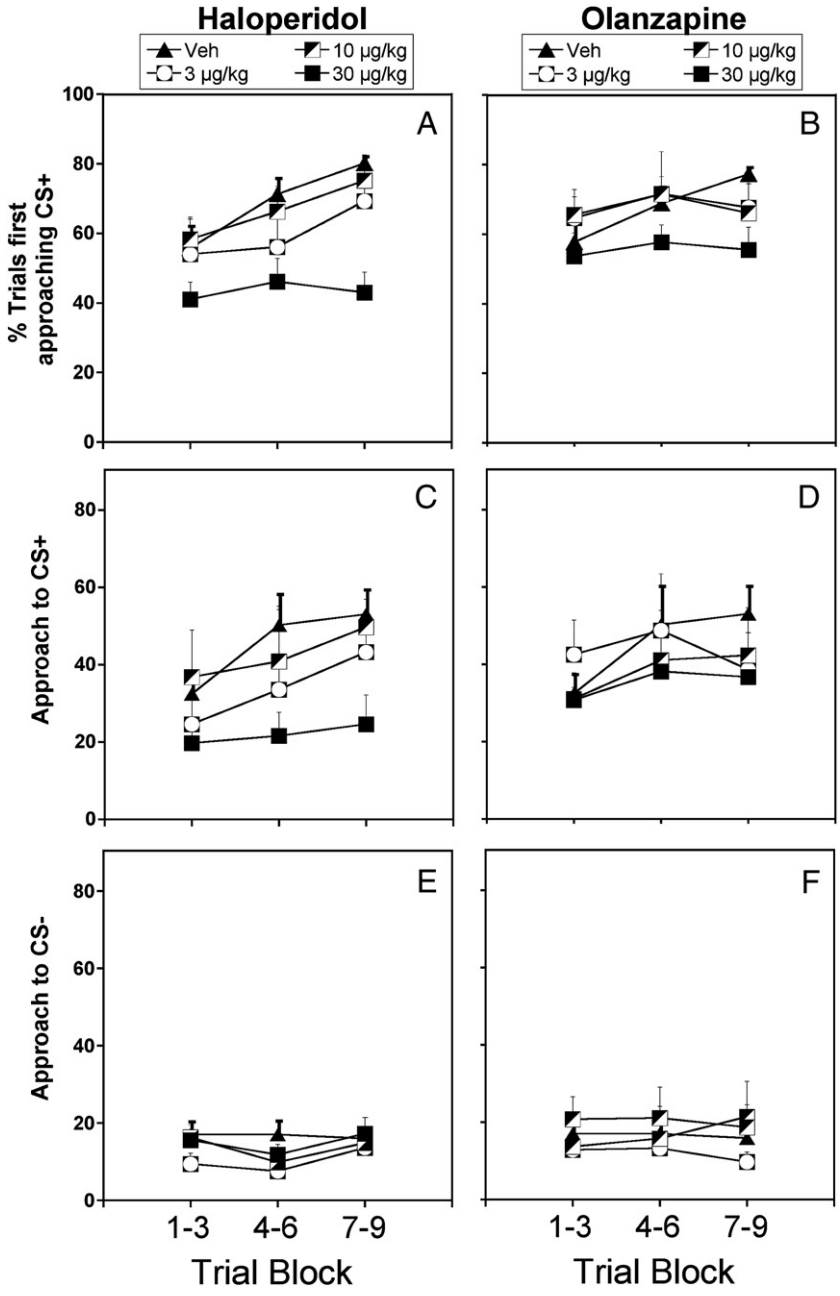

Fig. 1. Haloperidol and olanzapine effects on approach to conditioned cues during autoshaping. Panels A, B; percentage of trials in which the CS+ cue light was the first to be approached during cue presentation. Panels C, D; total number of approaches to CS+ light during CS+ presentation. Panels E, F; total number of approaches to CS− light during CS− presentation. Subjects given 100 µg/kg of haloperidol or olanzapine did not respond to the conditioning cues or UCS cues so this dose was excluded from the plot and analyses. The number of animals per group for both haloperidol and olanzapine are the following; $n = 13$, 6, 7 and 8 for veh, 3, 10, and 30 µg/kg doses, respectively. Each point represents the average number of approaches during each of the 3 sessions (±S.E.M).

performance) at 30 µ/kg followed by dramatic reduction of task performance at the 100 µg/kg dose (not included in this analysis or plots). Fig. 1E shows that there were few approaches to the CS− light during the acquisition phase from any group. There was no significant effect of dose on the number of approaches to the CS−.

3.1.2. Conditioned approach to US

In order to compare conditioned approach to the US (goal-track) to conditioned approach to the CS (sign-track) the difference score (approach during CS+ minus approach during CS−) for each endpoint following haloperidol administration is shown in the left and right side of Fig. 2A. Difference scores increased across training trials in the vehicle treated animals for approach to US and CS. Haloperidol altered the conditioned approach to the CS ($F(\text{Dose}) = p < 0.06$; vehicle versus 30 µg/kg, $p < 0.001$) but not conditioned approach to the US. Animals learned that the CS+ predicted reward delivery as demonstrated by increasing conditioned approach to the trough during the CS+ presentation across training trials ($F(\text{Trial}) = 11.57$; $\text{df} = 2, 17$, $p < 0.0007$). However, the difference score or the absolute number of entries during the CS+ or CS− presentation was not altered by haloperidol administration.

3.2. Olanzapine

The effect of olanzapine administration on acquisition of an autoshaping task is shown in Fig 1B,D,F. As with haloperidol, subjects administered the highest dose of olanzapine, 100 µg/kg, did not approach the cue lights (data not shown) and showed even less

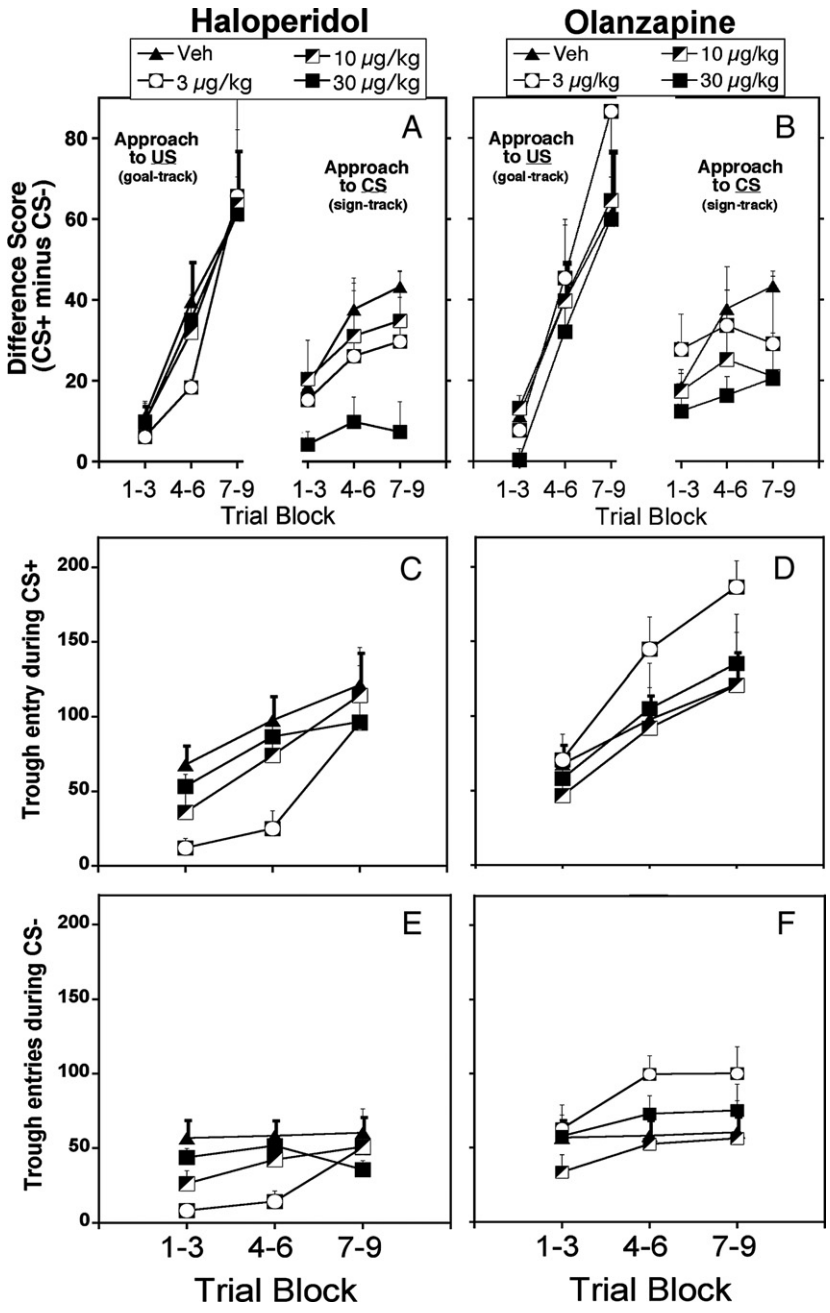

Fig. 2. Haloperidol and olanzapine effects on approach to US during conditioning cue presentation during autoshaping. Panels A, B; difference score (CS+ minus CS−) for the number of approaches to the US (goal-tracking) and CS (sign-tracking) during cue presentation. Panels C, D; total number of approaches to US during CS+ presentation. Panels E, F; total number of approaches to US during CS− presentation. Subjects given 100 μg/kg of haloperidol or olanzapine did not respond to the conditioning cues or UCS cues so this dose was excluded from evaluation. The number of animals per group for both haloperidol and olanzapine are the following; $n = 13, 6, 7$ and 8 for veh, 3, 10, and 30 μg/kg doses, respectively. Each point represents the mean ± S.E.M.

exploration of the pellet dispenser than did the haloperidol group at the same dose. As a result of this impairment, the 100 μg/kg dose was excluded from all subsequent evaluation.

3.2.1. Conditioned approach to CS

Rats treated with the olanzapine vehicle showed a significant increase in approaches to the positive cue as a function of exposure to the cue-reward pairing. The percentage of approaches which were made to the CS+ cue first during its presentation changed as a function of trial across the acquisition phase of autoshaping ($F(\text{Trial}) = 5.17$; $df = 2, 11$, $p < 0.03$) (Fig. 1B). In contrast to haloperidol, olanzapine did not show a significant dose-dependent disruption of autoshaping. However, given the importance of this comparative finding, the lack of difference found between drugs in the three-way ANOVA (see above) and the general impression from Fig. 1 that olanzapine altered autoshaping, further analysis was conducted. All doses of olanzapine diminished to a non-significant level the trend across trials for increased approach to the CS+ as measured by percent first approach and total approaches. The 30 μg/kg dose of olanzapine did not depress the formation of conditioned approach as much as the same dose of haloperidol. However, this dose approached significance when compared alone to vehicle ($p < 0.07$). Thus, similar in profile to haloperidol's effect, as dose is increased there is a slight but non-significant reduction in CS+ incentive value at the 3 and 10 μg/kg dose, then near elimination of cue incentive value without altering task performance at 30 μ/kg ($p < 0.07$) followed by dramatic reduction of task performance at the

100 µg/kg dose (not included in this analysis or plots). Fig. 1E shows there was no significant effect of dose on the number of approaches to the CS−.

3.2.2. Conditioned approach to US

In order to compare conditioned approach to the US (goal-track) to conditioned approach to the CS (sign-track) the difference score (approach during CS+ minus approach during CS−) for each endpoint following olanzapine administration is shown in the left and right sides of Fig. 2B. Difference scores increased across training trials for both US and CS approaches. Olanzapine altered the conditioned approach to the CS (F(Dose) = p<0.09; vehicle versus 30 µg/kg, p<0.019) but not conditioned approach to the US . As was true for haloperidol, olanzapine treated animals learned the association between CS+ presentation and reward delivery as evidenced by increasing conditioned approach to the trough during the CS+ presentation (F(Trial) = 38.94; df = 2, 21, p<0.00017) but again, the difference score or the absolute number of entries during the CS+ or CS− cue presentation was not significantly altered by olanzapine administration.

3.3. Drug comparison

3.3.1. Conditioned approach to CS

There was no overall difference between haloperidol and olanzapine on acquisition of autoshaping on any of the dependent variables (% first approach to CS+, CS+ approach, CS− approach, and difference score) as determined in three-way ANOVAs (Drug × Dose × Trial, comparing the left column to right column panels in Fig. 1 and Fig. 2A,B).

3.3.2. Conditioned approach to US

Olanzapine treated rats approached the trough more frequently than the haloperidol treated rats during presentation of both the CS+ (F(Drug) = 4.82; df = 1, 43, p<0.034) and CS− (F(Drug) = 7.86; df = 1, 43, p<0.008). The difference between drugs in approaches to the CS+ was not dose sensitive. However, there was a marginal interaction between dose and drug for approaches to the CS− (F(Dose × Drug) = 2.56; df = 3, 43, p<0.067). Since trough entries in olanzapine treated rats were indiscriminately greater during both CS+ and CS− cue presentation than the haloperidol treated rats there was no main effect of drug using difference score (CS+ minus CS−) as a dependent variable. The fact that olanzapine treated rats entered approached the trough more during CS+ and CS− presentation suggests that haloperidol may have had a slightly greater motoric effect, however this conclusion is not supported by the lack of difference on approach to the conditioned cues.

3.4. Amphetamine-induced disruption of PPI

Presentation of weak prepulse stimuli (1, 3, 6, 12 or 15 dB above the 65 dB background) 100 ms prior to the startle stimulus (120 dB) diminished startle amplitude in a stimulus-intensity dependent manner in vehicle treated rats (F(Intensity) = 15.7, p<.0002). A significant startle response to the prepulse stimuli was not observed at any of the prepulse stimulus intensities. The protocol used in these studies often times resulted in modest prepulse facilitation (approx. 20%) at the lower prepulse stimulus intensities.

3.4.1. Amphetamine-induced disruption of PPI

Fig. 3 shows the disruptive effects of amphetamine on sensorimotor gating. Amphetamine diminished prepulse inhibition (F(AMPH) = 4.4, p<0.05). Since amphetamine diminished PPI in a parallel manner across all stimulus intensities (F(Intensity × AMPH) = 0.03, p<0.99) the average PPI is shown. The vehicle groups for haloperidol and olanzapine did not differ significantly therefore the groups were combined for graphical representation. Amphetamine did not significantly alter startle amplitude or habituation to startle across trials.

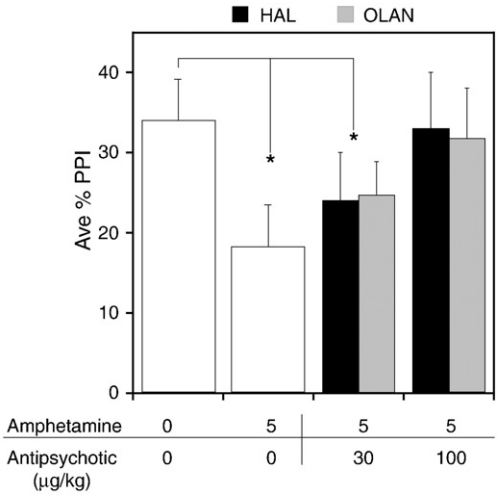

Fig. 3. HAL and OLAN effect on AMPH-induced disruption of PPI. Amphetamine administration significantly reduced sensorimotor gating (%PPI). Haloperidol and olanzapine did not reverse the gating deficit at 30 µg/kg but restored normal function at 100 µg/kg. Each bar represents the mean (±S.E.M) of 7–10 subjects.

3.4.2. Antipsychotic antagonism of amphetamine-induced disruption of PPI

Fig. 3 shows the effects of haloperidol and olanzapine on amphetamine-induced disruption of PPI. Haloperidol and olanzapine returned the gating deficit induced by amphetamine (second bar) back to control levels (compare to last set of bars, 100 µg/kg). Haloperidol and olanzapine at the highest dose (100 µg/kg) significantly improved PPI compared to the amphetamine treated animals (F(HAL) = 4.3, p<0.05; F(OLAN) = 4.6, p<0.05) while the lower dose tested for each drug (30 µg/kg) had no significant effect. Olanzapine did not significantly alter startle amplitude or habituation to startle across trials in amphetamine treated animals. Olanzapine alone did not alter startle amplitude or habituation to startle across trials when compared to vehicle treated animals.

4. Discussion

Autoshaping is a behavioral paradigm uniquely suited to quantify the degree to which a reward-predictive cue has acquired incentive motivational value. Given the strong role of the mesolimbic dopamine system and the potential involvement of additional neurochemical systems in autoshaping (Dalley et al., 2005; Day et al., 2007; Di Ciano et al., 2001; Parkinson et al., 2002; Tomie et al., 2000) the present study sought to investigate potential differences between widely used typical (haloperidol) and atypical (olanzapine) antipsychotics on incentive salience attribution. In addition, characterization of effective dosing levels in a model used to probe therapeutic efficacy in schizophrenia (PPI) was conducted in order to provide a comparison of the dose threshold at which antipsychotics may interfere with reward processing versus potential therapeutic efficacy. Surprisingly, both drugs severely disrupted incentive salience transfer at doses well below those presumed necessary for therapeutic efficacy (Kapur et al., 2003) and to be effective in alleviating the therapeutically relevant measure of amphetamine-induced disruptions in sensorimotor processing.

A primary mechanism thought to be responsible for amelioration of delusions and psychosis in schizophrenia is their DRD2 antagonist properties (Kapur and Remington, 2001; Kapur et al., 2000). Unfortunately, the primary mechanism thought to be responsible for neuroleptic-induced dysphoria is their DRD2 antagonist properties

as well (Heinz et al., 1998; Mizrahi et al., 2007). Antipsychotic drugs occupy approximately 65–85% of the DRD2 receptor at effective therapeutic doses (Kapur et al., 2003). In rats, a dose of haloperidol between 40 and 80 μg/kg is required to achieve this level of receptor occupancy compared to a 1–2 mg/kg dose for olanzapine. Haloperidol and olanzapine disrupt autoshaping below these respective dose ranges. The dose of haloperidol that altered induction of incentive salience in the current study (30 μg/kg) results in approximately 60% receptor occupancy. In contrast, the dose of olanzapine that altered induction of incentive salience (30 μg/kg) results in less than 5% receptor occupancy. Two methods can be used to compare the effects of olanzapine and haloperidol on reward processing versus therapeutic efficacy: the 'therapeutic index' using (i) the threshold dose disrupting autoshaping (30 μg/kg) versus the dose required for therapeutic drug levels (40 and 1000 μg/kg for haloperidol and olanzapine, respectively) and (ii) the threshold dose disrupting autoshaping (30 μg/kg) versus the dose that ameliorates amphetamine-induced disruptions in sensorimotor gating (100 μg/kg for both drugs). Both metrics suggests that haloperidol and olanzapine disrupt the transfer of incentive salience to reward-predictive cues at doses well below that required to ameliorate amphetamine-induced alteration of PPI and to achieve what has been proposed as clinically relevant receptor occupancy, however olanzapine produced disruption at lower receptor occupancy. Under these conditions, the therapeutic index (undesired effect (incentive learning)/desired effect (PPI, receptor occupancy)) is in fact more favorable for haloperidol than olanzapine. Future studies will be required to confirm this observation and determine its generality in additional reward paradigms.

Haloperidol and olanzapine attenuated approach to the CS+ cue (sign-tracking) during acquisition yet exploration of the pellet dispenser during CS+ presentation (goal-tracking) and pellet consumption was not altered by haloperidol or olanzapine, until the highest tested dose (100 μg/kg). As the antipsychotic dose was increased (3, 10, 30 μg/kg) the threshold for disrupting sign-tracking was reached prior to the threshold for disrupting goal-tracking (100 μg/kg). The specific aspects of reward processing that are blocked by neuroleptics are critically dependent upon the experimental design (see (Blackburn et al., 1987; Dickinson et al., 2000). Day et al. (2007) provide a neurochemical framework to explain the disruption in incentive salience transfer observed in autoshaping. Using fast-scan cyclic voltammetry they demonstrate that during acquisition of autoshaping dopamine phasically increases during reward presentation as well as CS+ and CS− stimuli (non-selectively) then shifts to selective phasic increase during CS+ presentation in later trials. Under these conditions, haloperidol and olanzapine would block the post-synaptic consequences of dopamine released during cue and primary reward presentation and the downstream effects that play a role in the generation of incentive motivational salience to the reward-predictive cue. Since both phasic dopamine events were blocked it is not clear whether reward- or cue-induced (or both) release is critical to incentive salience attribution under these conditions (Berridge, 2007; Wise, 2008). Regardless, the current results provide evidence to suggest that incentive salience attribution to reward-predictive cues is more sensitive to haloperidol and olanzapine than conditioned approach to or consumption of the primary reward. An interesting question for future investigation is whether or not discrete disruption of dopamine transmission during CS+ versus US would selectively alter goal versus sign-tracking and whether or not individual differences previously noted in goal- versus sign-tracking (Flagel et al., 2007) influence the disruptive effects of antipsychotics on reward processing.

A long-standing question in schizophrenia research is whether the reward deficits seen in schizophrenic patients are core features of the illness or a consequence of medication. Schizophrenic patients treated with antipsychotics have diminished anticipatory pleasure (Gard et al., 2007) and capacity to assign subjective value to potential outcomes despite normal self-reported reward sensitivity (Heerey et al., 2008; see Gold et al., 2008). In the current study, antipsychotic medication (in the low dose range tested) appears to produce a reward processing deficit that may parallel that seen in schizophrenic patients; both drugs blocked the attribution of incentive salience without altering conditioned approach to the reward or reward consumption. These results provide evidence to support a role for antipsychotics in the reward deficits observed in schizophrenic patients. However, there is evidence to suggest that even in unmedicated schizophrenic patients the presentation of reward-predictive cues results in less ventral striatal activation than controls (Juckel et al., 2006b) and there exists a diminished capacity to discriminate between motivationally salient and neutral stimuli (Murray et al., 2008). Thus, the reward deficits in incentive salience attribution can exist as a core feature of the illness-absent medication. Regardless of the relative contribution that core features of the illness versus antipsychotic medication make to anhedonia, the fact that antipsychotic medications compromise one of the most predictive measures of anhedonia, approach motivation (Germans and Kring, 2000), strongly indicates a need for improved medications to treat schizophrenia.

Overall, the evidence provided by these experiments provides a novel perspective on the effects of antipsychotic drugs in reward processing. The typical antipsychotic haloperidol and the atypical antipsychotic olanzapine significantly diminished the transfer of incentive motivational value to reward-predictive cues at doses below what is considered clinically relevant. Olanzapine disrupted this effect at doses that would result in significantly lower DRD2 occupancy. Both drugs diminished approach to stimuli predictive of reward at doses that did not alter conditioned approach to the US and reward consumption. The unique aspects of the autoshaping paradigm that enabled a separation of directed approach to cues associated with reward versus the reward itself provide a valuable platform to investigate antipsychotic drug effects.

Acknowledgments

This work was supported in part by NIMH Grant #R24MH072647 (J.M. Gold).

References

Awad AG, Voruganti LN. Impact of atypical antipsychotics on quality of life in patients with schizophrenia. CNS Drugs 2004;18:877–93.
Balsam PD, Fairhurst S, Gallistel CR. Pavlovian contingencies and temporal information. J Exp Psychol Anim Behav Process 2006;32:284–94.
Berridge KC. The debate over dopamine's role in reward: the case for incentive salience. Psychopharmacology (Berl) 2007;191:391–431.
Blackburn JR, Phillips AG, Fibiger HC. Dopamine and preparatory behavior: I. Eff Pimozide Behav Neurosci 1987;101:352–60.
Brown PL, Jenkins HM. Auto-shaping of the pigeon's key-peck. J Exp Anal Behav 1968;11:1–8.
Bymaster FP, Hemrick-Luecke SK, Perry KW, Fuller RW. Neurochemical evidence for antagonism by olanzapine of dopamine, serotonin, alpha 1-adrenergic and muscarinic receptors in vivo in rats. Psychopharmacology (Berl) 1996;124:87–94.
Dalley JW, Chudasama Y, Theobald DE, Pettifer CL, Fletcher CM, Robbins TW. Nucleus accumbens dopamine and discriminated approach learning: interactive effects of 6-hydroxydopamine lesions and systemic apomorphine administration. Psychopharmacology (Berl) 2002;161:425–33.
Dalley JW, Laane K, Theobald DE, Armstrong HC, Corlett PR, Chudasama Y, et al. Time-limited modulation of appetitive Pavlovian memory by D1 and NMDA receptors in the nucleus accumbens. Proc Natl Acad Sci U S A 2005;102:6189–94.
Day JJ, Roitman MF, Wightman RM, Carelli RM. Associative learning mediates dynamic shifts in dopamine signaling in the nucleus accumbens. Nat Neurosci 2007;10:1020–8.
Di Ciano P, Cardinal RN, Cowell RA, Little SJ, Everitt BJ. Differential involvement of NMDA, AMPA/kainate, and dopamine receptors in the nucleus accumbens core in the acquisition and performance of pavlovian approach behavior. J Neurosci 2001;21:9471–7.
Dickinson A, Smith J, Mirenowicz J. Dissociation of Pavlovian and instrumental incentive learning under dopamine antagonists. Behav Neurosci 2000;114:468–83.
Elmer GI, Pieper JO, Levy J, Rubinstein M, Low MJ, Grandy DK, et al. Brain stimulation and morphine reward deficits in dopamine D2 receptor-deficient mice. Psychopharmacology (Berl) 2005;182:33–44.

Everitt BJ, Dickinson A, Robbins TW. The neuropsychological basis of addictive behaviour. Brain Res Brain Res Rev 2001;36:129–38.
Flagel SB, Watson SJ, Robinson TE, Akil H. Individual differences in the propensity to approach signals vs goals promote different adaptations in the dopamine system of rats. Psychopharmacology (Berl) 2007;191:599–607.
Gamzu ER, Williams DR. Associative factors underlying the pigeon's key pecking in auto-shaping procedures. J Exp Anal Behav 1973;19:225–32.
Gard DE, Kring AM, Gard MG, Horan WP, Green MF. Anhedonia in schizophrenia: distinctions between anticipatory and consummatory pleasure. Schizophr Res 2007;93:253–60.
Germans MK, Kring AM. Hedonic deficit in anhedonia: support for the role of approach motivation. Personality Individ Differ 2000;28:659–72.
Gold JM, Waltz JA, Prentice KJ, Morris SE, Heerey EA. Reward processing in schizophrenia: a deficit in the representation of value. Schizophr Bull 2008;34: 835–47.
Heerey EA, Bell-Warren KR, Gold JM. Decision-making impairments in the context of intact reward sensitivity in schizophrenia. Biol Psychiatry 2008;64:62–9.
Heinz A, Knable MB, Coppola R, Gorey JG, Jones DW, Lee KS, et al. Psychomotor slowing, negative symptoms and dopamine receptor availability—an IBZM SPECT study in neuroleptic-treated and drug-free schizophrenic patients. Schizophr Res 1998;31: 19–26.
Hermann RC, Yang D, Ettner SL, Marcus SC, Yoon C, Abraham M. Prescription of antipsychotic drugs by office-based physicians in the United States, 1989–1997. Psychiatr Serv 2002;53:425–30.
Juckel G, Schlagenhauf F, Koslowski M, Filonov D, Wustenberg T, Villringer A, et al. Dysfunction of ventral striatal reward prediction in schizophrenic patients treated with typical, not atypical, neuroleptics. Psychopharmacology (Berl) 2006a;187:222–8.
Juckel G, Schlagenhauf F, Koslowski M, Wustenberg T, Villringer A, Knutson B, et al. Dysfunction of ventral striatal reward prediction in schizophrenia. Neuroimage 2006b;29:409–16.
Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am J Psychiatry 2003;160: 13–23.
Kapur S, Remington G. Dopamine D(2) receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient. Biol Psychiatry 2001;50:873–83.
Kapur S, Seeman P. Antipsychotic agents differ in how fast they come off the dopamine D2 receptors. Implications for atypical antipsychotic action. J Psychiatry Neurosci 2000;25:161–6.
Kapur S, Zipursky R, Jones C, Remington G, Houle S. Relationship between dopamine D (2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. Am J Psychiatry 2000;157:514–20.
Kapur S, VanderSpek SC, Brownlee BA, Nobrega JN. Antipsychotic dosing in preclinical models is often unrepresentative of the clinical condition: a suggested solution based on in vivo occupancy. J Pharmacol Exp Ther 2003;305:625–31.
King DJ, Burke M, Lucas RA. Antipsychotic drug-induced dysphoria. Br J Psychiatry 1995;167:480–2.
Lewander T. Neuroleptics and the neuroleptic-induced deficit syndrome. Acta Psychiatr Scand Suppl 1994;380:8-13.
Mizrahi R, Rusjan P, Agid O, Graff A, Mamo DC, Zipursky RB, et al. Adverse subjective experience with antipsychotics and its relationship to striatal and extrastriatal D2 receptors: a PET study in schizophrenia. Am J Psychiatry 2007;164:630–7.
Morimoto T, Hashimoto K, Yasumatsu H, Tanaka H, Fujimura M, Kuriyama M, et al. Neuropharmacological profile of a novel potential atypical antipsychotic drug Y-931 (8-fluoro-12-(4-methylpiperazin-1-yl)- 6H-[1]benzothieno[2, 3-b][1, 5] benzodiazepine maleate). Neuropsychopharmacology 2002;26:456–67.
Murray GK, Corlett PR, Clark L, Pessiglione M, Blackwell AD, Honey G, et al. Substantia nigra/ventral tegmental reward prediction error disruption in psychosis. Mol Psychiatry 2008;13(239):67–76.
Parkinson JA, Olmstead MC, Burns LH, Robbins TW, Everitt BJ. Dissociation in effects of lesions of the nucleus accumbens core and shell on appetitive pavlovian approach behavior and the potentiation of conditioned reinforcement and locomotor activity by D-amphetamine. J Neurosci 1999;19:2401–11.
Parkinson JA, Willoughby PJ, Robbins TW, Everitt BJ. Disconnection of the anterior cingulate cortex and nucleus accumbens core impairs Pavlovian approach behavior: further evidence for limbic cortical–ventral striatopallidal systems. Behav Neurosci 2000;114:42–63.
Parkinson JA, Dalley JW, Cardinal RN, Bamford A, Fehnert B, Lachenal G, et al. Nucleus accumbens dopamine depletion impairs both acquisition and performance of appetitive Pavlovian approach behaviour: implications for mesoaccumbens dopamine function. Behav Brain Res 2002;137:149–63.
Pellegrini S, Lopez Seal MF, Papini MR. Scaling relative incentive value: different adjustments to incentive downshift in pigeons and rats. Behav Process 2008;79: 182–8.
Phillips AG, McDonald AC, Wilkie DM. Disruption of autoshaped responding to a single of brain-stimulation reward by neuroleptic drugs. Pharmacol Biochem Behav 1981;14:543–8.
Rescorla RA, Solomon RL. Two-process learning theory: relationships between Pavlovian conditioning and instrumental learning. Psychol Rev 1967;74:151–82.
Robbins TW, Everitt BJ. Limbic-striatal memory systems and drug addiction. Neurobiol Learn Mem 2002;78:625–36.
Roiser JP, Stephan KE, den Ouden HE, Barnes TR, Friston KJ, Joyce EM. Do patients with schizophrenia exhibit aberrant salience? Psychol Med 2009;39:199–209.
Schlagenhauf F, Juckel G, Koslowski M, Kahnt T, Knutson B, Dembler T, et al. Reward system activation in schizophrenic patients switched from typical neuroleptics to olanzapine. Psychopharmacology (Berl) 2008;196:673–84.
Schwartz B, Gamzu E. Pavlovian control of operant behavior. In: Honig WK, Staddon JER, editors. Handbook of operant behavior. Englewood Cliffs, N.J.: Prentice-Hall; 1977. p. 53–97.
Seeman P, Van Tol HH. Dopamine receptor pharmacology. Trends Pharmacol Sci 1994;15:264–70.
Tomie A, Aguado AS, Pohorecky LA, Benjamin D. Individual differences in pavlovian autoshaping of lever pressing in rats predict stress-induced corticosterone release and mesolimbic levels of monoamines. Pharmacol Biochem Behav 2000;65: 509–17.
Tomie A, Grimes KL, Pohorecky LA. Behavioral characteristics and neurobiological substrates shared by Pavlovian sign-tracking and drug abuse. Brain Res Rev 2008;58:121–35.
Voruganti L, Cortese L, Oyewumi L, Cernovsky Z, Zirul S, Awad A. Comparative evaluation of conventional and novel antipsychotic drugs with reference to their subjective tolerability, side-effect profile and impact on quality of life. Schizophr Res 2000;43:135–45.
Wise RA. Dopamine and reward: the anhedonia hypothesis 30 years on. Neurotox Res 2008;14:169–83.