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Selective Alleviation of Compulsive Lever-Pressing in Rats by D_1, but not D_2, Blockade: Possible Implications for the Involvement of D_1 Receptors in Obsessive–Compulsive Disorder

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Rats undergoing extinction of lever-pressing for food after the attenuation of an external feedback for this behavior exhibit excessive lever-pressing unaccompanied by an attempt to collect a reward. This behavior may be analogous to the excessive and unreasonable behavior seen in obsessive–compulsive disorder. In the present study, we tested the hypothesis that the compulsive behavior induced by signal attenuation is mediated via D_1 rather than D_2 receptors. Administration of 0.005, 0.01 and 0.03 mg/kg of the D_1 antagonist SCH 23390 reduced the number of compulsive lever-presses without affecting the number of lever-presses followed by an attempt to collect a reward. In contrast, administration of 0.005, 0.01, 0.024, 0.036 and 0.05 of the D_2 antagonist haloperidol dose-dependently decreased both types of lever-presses. In addition, haloperidol at doses that decreased lever-pressing in the post-training signal attenuation procedure (0.036 and 0.05 mg/kg) had a similar effect in regular extinction, whereas an SCH 23390 dose that decreased compulsive lever-pressing in the post-training signal attenuation procedure (0.01 mg/kg) had no effect on regular extinction. On the basis of electrophysiological data on the response of dopamine neurons to the omission of an expected reward, these results were interpreted as suggesting that compulsive lever-pressing depends on a phasic decrease in the stimulation of D_1 receptors. The implications of these results for the pathophysiology and treatment of obsessive–compulsive disorder are discussed.
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INTRODUCTION

Obsessive–compulsive disorder (OCD) is a psychiatric affliction with a lifetime prevalence of 1–3% (Rasmussen and Eisen, 1992; Sasson *et al*, 1997). The fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM IV) classifies OCD as an anxiety disorder characterized by obsessive thinking and compulsive behavior (eg doubting, checking or washing). A major characteristic of obsessions and compulsions is that they are excessive and unreasonable (DSM IV). The findings that serotonin reuptake inhibitors (SRIs) are effective in alleviating obsessions and compulsions in patients (Zohar and Insel, 1987; Zohar *et al*, 1992) have directed much attention to the involvement of the serotonergic system in the pathophysiology of OCD (for a review, see Sasson and Zohar, 1996; Stein, 2000). Abnormalities of the dopaminergic system, however, have also been implicated in OCD on the basis of several lines of clinical and preclinical evidence (Goodman *et al*, 1990; McDougle *et al*, 1993). These include the high incidence of obsessive–compulsive behavior in a number of basal-ganglia-related disorders, such as Tourette's syndrome (Frankel *et al*, 1986; Grad *et al*, 1987; Pitman *et al*, 1987), and encephalitis lethargica (Von Economo's encephalitis; Jelliffe, 1932), changes in obsessive–compulsive symptoms following the administration of amphetamine and cocaine to OCD patients (Insel *et al*, 1983; Leonard and Rapoport, 1987; McDougle *et al*, 1989), the surplus therapeutic benefits obtained with coadministration of SRIs and dopaminergic blockers (McDougle *et al*, 1990, 1994; Sasson and Zohar, 1996; Saxena *et al*, 1996), and the emergence of compulsive-like behaviors in humans and animals following the administration of amphetamine (Ellinwood, 1967; Satel and McDougle, 1991; Schiorring, 1975).

In the present study, we sought to test the involvement of dopamine receptors in the production of compulsive behavior using a novel rat model of OCD. The model was developed on the basis of two assumptions made with regard to obsessions and compulsions: (1) they are an exaggeration of normal thoughts and behaviors (Pitman, 1989; Rasmussen and Eisen, 1992; Reed, 1985), and (2) they result from a failure to cease responding following the

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successful completion of an action owing to a deficient response feedback mechanism (eg Baxter, 1999; Gray, 1982; Malloy, 1987; Pitman, 1991; Reed, 1977; Otto, 1990, 1992).

The model simulates the deficiency in response feedback hypothesized to underlie obsessions and compulsions. The deficiency is induced using the paradigm of post-training signal attenuation, and leads to a pattern of lever-press responding that may be analogous to compulsive behavior. The procedure includes four stages. In stage 1, a compound stimulus is established as a signal for the delivery of food by classically conditioning it with food. In stage 2, rats are trained to lever-press for food whose delivery is accompanied by the compound stimulus. Thus, the stimulus is established as a feedback signaling that the lever-press response was effective in producing food. In stage 3, signal attenuation, the capacity of the signal to serve as a feedback for the effectiveness of the lever-press response is attenuated by extinguishing the classical contingency between the stimulus and food. In the last stage, the test stage, rats lever-press behavior is assessed under extinction conditions (ie pressing the lever results in the presentation of the stimulus, but no food is delivered).

We found that during the test stage rats exhibited a period of excessive lever-pressing that was highly correlated with trials on which no attempt was made to collect a reward. Importantly, this correlation was not evident in regular extinction of the lever-press behavior (ie a test stage not preceded by signal attenuation), although regular extinction also increased lever-pressing (Joel and Avisar, 2001). The cessation of the attempts to collect a reward, which indicates that the rat detected the change in response consequences, combined with the increased emission of the lever-press response, makes the operant behavior both excessive and 'inappropriate' or 'unreasonable,' thus fulfilling two important criteria of compulsive behavior (DSM IV; Rapoport, 1989; Reed, 1985). In support of the relevance of compulsive lever-pressing to OCD, we showed that this behavior is abolished by the SRI fluoxetine but not by the anxiolytic drug diazepam (Joel and Avisar, 2001), in accordance with the differential efficacy of these drugs in alleviating obsessions and compulsions in OCD patients (eg Dolberg *et al*, 1996; Zohar *et al*, 1992), and is enhanced following lesion to the orbital cortex (Joel *et al*, submitted), in line with findings implicating orbitofrontal cortex dysfunction in OCD patients (Saxena *et al*, 1998).

In a recent study, we found evidence for the involvement of DA mechanisms in the induction of compulsive behavior in the model (Joel *et al*, 2001). Thus, rats response to signal attenuation was enhanced following repeated administration of the D_1 antagonist SCH 23390 or the D_2 agonist quinpirole during lever-press training. Conversely, the repeated administration of the D_1 agonist SKF 38393 or the D_2 antagonist haloperidol had no effect on rats behavior in the test. On the basis of data regarding the effects of chronic treatment with dopaminergic agents, these results were interpreted as suggesting that the behavioral response to signal attenuation is mediated via D_1 rather than D_2 receptors (Joel *et al*, 2001). In the present study we tested this hypothesis by assessing the effects of blockade of D_1 or D_2 receptors during the test stage on compulsive lever-pressing. Since D_1 and D_2 antagonists are known to reduce lever-pressing for food (Beninger and Miller, 1998), the critical question was not whether these compounds reduce compulsive lever-pressing, but rather whether there are doses at which such reduction is restricted to compulsive lever-presses (ie lever-presses not followed by an attempt to collect a reward) without concomitantly affecting lever-presses that are followed by an attempt to collect a reward.

Experiment 1 tested the effects of the D_1 antagonist SCH 23390 (0.005, 0.01, and 0.03 mg/kg). It should be noted that SCH 23390 binds with high affinity to 5-HT_{2A} receptors (Bischoff *et al*, 1986). However, the doses used in the present experiment are thought to be selective for the D_1 class and to avoid the interactions with 5-HT_{2A} receptors found at higher doses (Bischoff *et al*, 1986; Hess *et al*, 1986). Experiment 2 tested the effects of the D_2 antagonist haloperidol (0.005, 0.01, and 0.05 mg/kg). Since the two lower doses of haloperidol had no effect, and the highest dose disrupted responding altogether, experiment 3 tested two additional doses of haloperidol (0.024 and 0.036 mg/kg). To test whether drug effects in experiments 1–3 were specific to the behavioral response to signal attenuation, experiment 4 tested the effects of SCH 23390 (0.01 mg/kg) and haloperidol (0.036 and 0.05 mg/kg) on extinction of the lever-press response that was not preceded by signal attenuation. It was expected that a dose that selectively reduces compulsive lever-pressing in the post-training signal attenuation procedure would have no effect on regular extinction, whereas a dose that reduces both types of lever-presses in the post-training signal attenuation procedure would have a similar effect on regular extinction.

MATERIALS AND METHODS

Subjects

Male Wistar rats (Tel Aviv University, Sackler Faculty of Medicine, Israel) approximately 3 months old, weighing 300–420 g, were housed four in a cage under a reversed 12-h light–dark cycle (lights on 1900–0700 h). Rats were maintained on a 22-h food restriction schedule (see below), with water freely available. They were weighed twice a week to ensure that their body weight was not reduced to below 90%. All animal research was carried out according to the guidelines of the Institutional Animal Care and Use Committee of Tel Aviv University.

Apparatus

Behavioral testing was conducted in four operant chambers (Campden Instruments, Loughborough, UK) fitted with a food magazine and two retractable levers. The levers were 4 cm wide and were positioned 2.8 cm from the side walls, 7.5 cm from either side of the food magazine, and 5 cm from the grid floor. The chambers could be illuminated by a houselight located at the ceiling. Access to the food magazine was through a hinged Perspex panel, the opening of which activated a microswitch. The food magazine could be illuminated by a 3-W light. An 80-dB, 2.8-kHz tone was produced by a Sonalert module (Model SC 628). A food dispenser delivered 45-mg, dust-free Noyes pellets (Sandown Chemical Ltd, Hampton, England). The operant chambers were housed in sound-attenuating boxes, and

ventilating fans were mounted on the side of each box. Equipment programming and data recording were computer controlled.

Procedure

Handling Before the beginning of the experiment, rats were handled for about 2 min daily for 5 days. A 22-h food restriction schedule began simultaneously with handling and continued throughout behavioral testing. Food was provided in the home cage between 1400 and 1600 h, at least half an hour after the end of the session. On the last 2 days, after handling, 20–30 food pellets used as reinforcement for operant training were introduced into the home cages on a tray. The tray was removed from the cage after each rat was observed to consume at least two pellets.

Stage 1: Magazine Training

On days 1–3, rats were trained to collect food pellets from the food magazine in the operant chamber, with the levers retracted. On the first day of magazine training, six food pellets were placed in the food magazine, and training began after each of the four rats had collected its food pellets. At the start of each trial, the houselight was turned on. After a 5-s variable delay, a single food pellet was dropped into the food magazine, simultaneous with the onset of a compound stimulus consisting of the magazine light and a tone. The compound stimulus and houselight were turned off after the rat's head entered the food magazine or after 15-s had elapsed. Each trial was followed by a 30-s intertrial interval. Each rat was trained until it completed 30 trials in which it inserted its head into the food magazine during stimulus presentation, or until a total of 40 trials was reached.

Stage 2: Lever-Press Training

Rats were trained to lever-press in a discrete-trial procedure. The start of each trial was signaled by the onset of the houselight. After 5-s, both levers were inserted into the chamber; responding on one of them (reinforced lever, RL) resulted in the delivery of a single food pellet into the magazine, accompanied by the presentation of the compound stimulus. The levers were retracted, and the compound stimulus and houselight were turned off, after the rat's head entered the food magazine or after 15-s had elapsed. Responding on the other lever (nonreinforced lever, NRL) had no programmed consequences. The lever designated as RL was counterbalanced over subjects and remained the same for each rat over the entire experimental procedure. Each trial was followed by a 30-s intertrial interval. On day 4, each rat was trained until it completed 24 trials (that is, the rat pressed the lever and inserted its head into the food magazine during stimulus presentation (see below)) or until a total of 60 trials was reached. Rats that failed to attain at least 20 completed trials were returned to the test chamber at the end of the day for an additional session. Rats that did not attain at least 20 completed trials in the second session were excluded from the experiment. On days 5 and 6, all rats were trained as on day 4, except that training ended when the rat had attained 40 completed trials or when a total of 60 trials was reached. The following measures were recorded: (a) the number of trials on which the rat did not press the RL (unpressed trials); (b) the number of trials on which the rat pressed the RL and inserted its head into the food magazine to collect the food reward (completed trials); (c) the number of trials on which the rat pressed the RL without inserting its head into the food magazine (uncompleted trials); (d) the number of lever-presses on the NRL; (e) the number of presses after the first response on the RL (extra lever-presses, ELP) in uncompleted trials (ELP-U); and (f) the number of ELP in completed trials (ELP-C).

Stage 3: Signal Attenuation

On days 7–9, with the levers retracted, rats were exposed to the presentation of the compound stimulus as on days 1–3, but no food was delivered to the food magazine, and the compound stimulus was turned off after 10-s instead of after 15-s. Rats received 30 such trials on each day. In experiment 4 (regular extinction), rats were brought to the laboratory and left in their home cages for a period equivalent to the average duration of the signal attenuation stage.

Stage 4: Test

On day 10, rats were trained as in the lever-press training stage, except that no food was delivered to the food magazine; that is, pressing the lever resulted in the presentation of the compound stimulus only. The session lasted for 50 trials.

Drugs

Drugs were administered intraperitoneally in a volume of 1 ml/kg 60 min before the beginning of the test stage. Haloperidol, prepared from an ampoule containing 5 mg haloperidol in 1 ml of solvent that contained 6 mg lactic acid (Janssen-Cilag, Berchem, Belgium) and diluted with saline, was administered at a dose of 0.005, 0.01, 0.024, 0.036 and 0.05 mg/kg. SCH 23390 (Sigma Chemical, Rehovot, Israel), dissolved in 0.3% tartaric acid and diluted with saline, was administered at a dose of 0.005, 0.01 and 0.03 mg/kg. Doses were selected on the basis of previous studies that showed disruption of lever-press behavior by these drugs (haloperidol: Fowler and Liou, 1998; Salamone *et al*, 1996; SCH 23390: Beninger *et al*, 1987; Cousins *et al*, 1994; Fowler and Liou, 1998). In addition, in a preliminary study, we found that 0.10 mg/kg haloperidol and 0.05 mg/kg SCH 23390 abolished responding in lever-press training sessions. No drug controls received an equivalent volume of the corresponding vehicle.

Statistical Analysis

Analyses of variance (ANOVAs) with a main factor of drug were performed on the number of completed trials, uncompleted trials, ELP-C and ELP-U in the test. (The number of unpressed trials was not analyzed because in the test stage the number of completed trials, uncompleted trials and unpressed trials always sums up to 50). Significant drug effects were followed by *post hoc* comparisons of each of the drug-treated groups with the vehicle group. For all comparisons, significance was assumed at $p < 0.05$.

RESULTS

Experiment 1: Effects of 0.005, 0.01 and 0.03 mg/kg SCH 23390 in the Post-Training Signal Attenuation Procedure

A total of 28 rats were randomly assigned to four groups (vehicle, 0.005, 0.01 and 0.03 mg/kg SCH 23390). Two rats needed an additional session on day 4.

Figures 1a–d present the mean and standard error of the total number of completed trials, uncompleted trials, ELP-C and ELP-U, respectively, in the four groups on the test day. As can be seen, there were no differences between the groups in the number of completed trials or in the number of ELP-C: $F(3,24) = 0.68$, $p > 0.5$ and $F(3,24) = 0.27$, $p > 0.8$, respectively. The three groups treated with SCH 23390 had fewer uncompleted trials and fewer ELP-U than the vehicle-treated group: $F(3,24) = 3.06$, $p < 0.05$ and $F(3,24) = 2.435$, $p < 0.09$, respectively. *Post hoc* least significant difference (LSD) comparisons indicated a significant difference between each of the SCH 23390-treated groups and the vehicle group on both measures ($p < 0.05$).

Experiments 2 and 3: Effects of 0.005, 0.01, 0.024, 0.036 and 0.05 mg/kg Haloperidol in the Post-Training Signal Attenuation Procedure

In experiment 2, 28 rats were randomly assigned to four groups (vehicle, 0.005, 0.01 and 0.05 mg/kg haloperidol). Two rats did not attain the criterion of 20 completed trials in the second session of day 4 and were excluded from the experiment. In experiment 3, 24 rats were randomly assigned to three groups (vehicle, 0.024 and 0.036 mg/kg haloperidol). Two rats did not attain the criterion of 20 completed trials in the second session of day 4 and were excluded from the experiment. Since there were no significant differences between the vehicle groups in the two experiments ($p > 0.2$), the data from the two experiments were combined. Thus, the final analysis included 13, 7, 6, 7, 8 and 7 rats in the vehicle, 0.005, 0.01, 0.024, 0.036 and 0.05 mg/kg haloperidol groups, respectively.

Figures 2a–d present the mean and standard error of the total number of completed trials, uncompleted trials, ELP-C and ELP-U, respectively, in the six groups on the test day. As can be seen, the highest dose of haloperidol (0.05 mg/kg) caused a significant decrease in the number of completed trials, whereas the other doses had no effect, $F(5,41) = 2.87$, $p < 0.05$. (*Post hoc* LSD comparisons indicated a significant difference between the vehicle group and the 0.05 mg/kg haloperidol-treated group only, $p < 0.001$). Similarly, only the highest dose of haloperidol affected the number of uncompleted trials, $F(5,41) = 2.80$, $p < 0.05$. (*Post hoc* LSD comparisons indicated a significant difference between the vehicle group and the 0.05 mg/kg haloperidol-treated group only, $p < 0.05$; the effect of 0.036 mg/kg haloperidol did not reach significance, $p = 0.1$). Haloperidol's effects on the number of ELP-C and on the number of ELP-U were also dose dependent. Only the highest doses of haloperidol affected the number of ELP-C, $F(5,41) = 3.16$, $p < 0.05$ (*post hoc* LSD comparisons indicated a significant difference

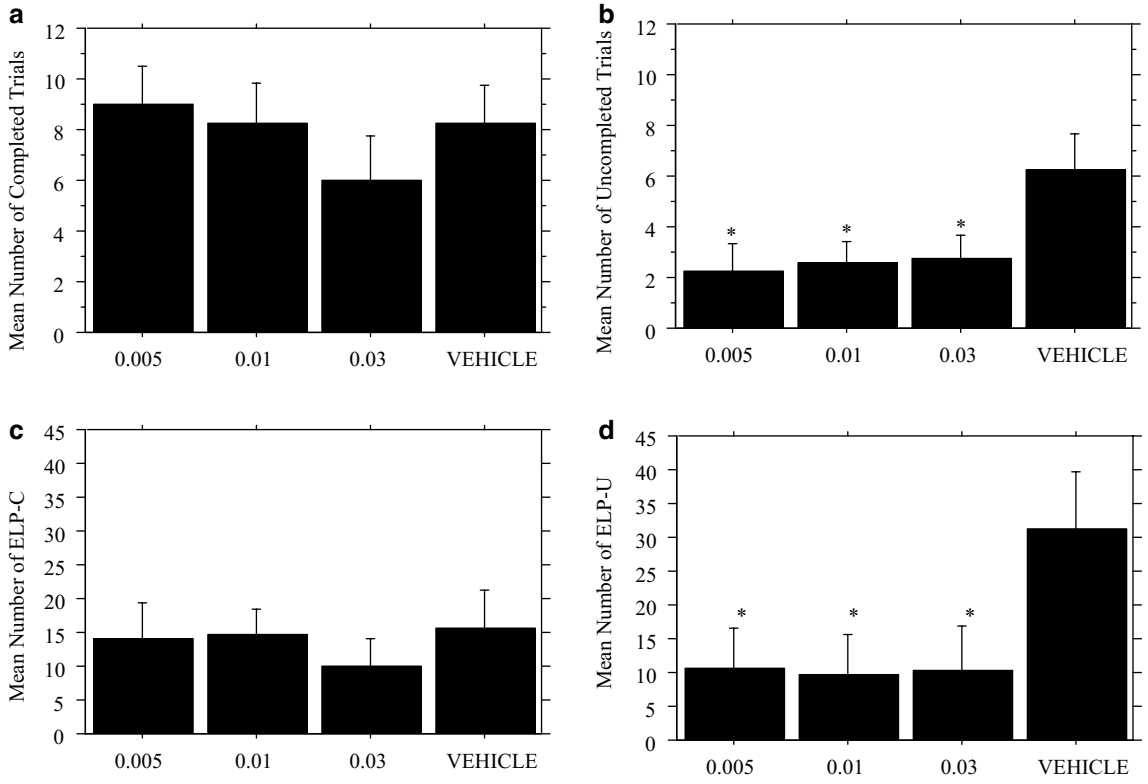

Figure 1 Mean and standard error of the number of (a) completed trials, (b) uncompleted trials, (c) ELP-C and (d) ELP-U on the test day of rats treated with vehicle, 0.005, 0.01 or 0.03 mg/kg SCH 23390 in the post-training signal attenuation procedure.

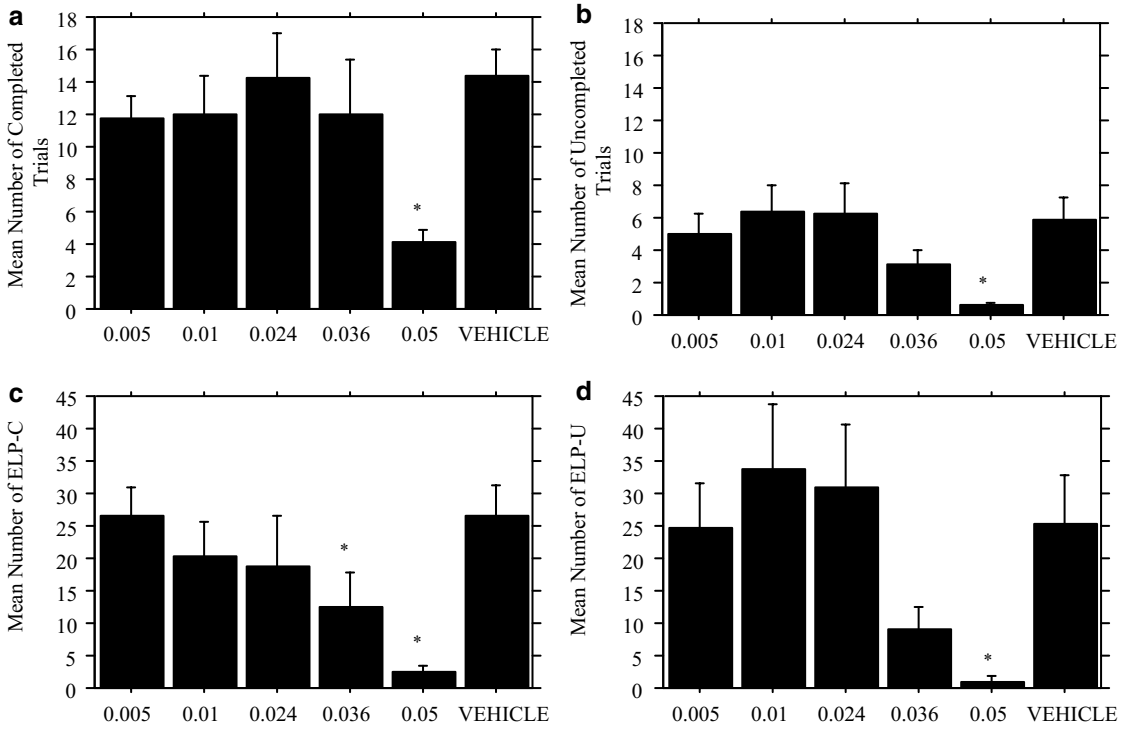

Figure 2 Mean and standard error of the number of (a) completed trials, (b) uncompleted trials, (c) ELP-C and (d) ELP-U on the test day of rats treated with vehicle, 0.005, 0.01, 0.024, 0.036 or 0.05 mg/kg haloperidol in the post-training signal attenuation procedure.

between the vehicle group and the 0.05 and 0.036 mg/kg haloperidol-treated groups only; $p<0.05$), and of ELP-U, $F(5,41)=2.69$, $p<0.05$ (*post hoc* LSD comparisons indicated a significant difference between the vehicle group and the 0.05 mg/kg haloperidol-treated group only, $p<0.05$, and a nearly significant difference between the vehicle group and the 0.036 mg/kg haloperidol group, $p=0.086$).

Experiment 4: Effects of 0.01 mg/kg SCH 23390 and 0.036 and 0.05 mg/kg Haloperidol in Regular Extinction

The aim of this experiment was to test the effects of SCH 23390 and haloperidol in a test stage not preceded by signal attenuation (ie in regular extinction). As the three SCH 23390 doses tested were effective in selectively reducing ELP-U, only the middle dose (0.01 mg/kg) was tested here. Since only two of the five haloperidol doses tested had an effect in the post-training signal attenuation procedure, only these two doses (0.036 and 0.05 mg/kg) were tested.

A total of 32 rats were randomly assigned to four groups (vehicle; 0.01 mg/kg SCH 23390; and 0.036 and 0.05 mg/kg haloperidol). Two rats did not learn to approach the food magazine during stage 1 and were excluded from the experiment. Five rats needed an additional session on day 4; two of these rats did not attain the criterion of 20 completed trials in the second session and were excluded from the experiment. Thus, the final analysis included seven rats in each group.

Figures 3a–d present the mean and standard error of the total number of completed trials, uncompleted trials, ELP-C and ELP-U, respectively, in the four groups on the test day. As can be seen, haloperidol decreased the number of completed trials, whereas SCH 23390 had no effect, $F(3,23)=14.64$, $p<0.0001$. (*Post hoc* LSD comparisons indicated a significant difference between the vehicle group and the 0.05 and 0.036 mg/kg haloperidol-treated groups only, $p<0.001$). Haloperidol at 0.05 mg/kg but not 0.036 mg/kg (and not SCH 23390) also decreased the number of uncompleted trials, but this effect did not reach statistical significance, $F(3,23)=1.25$, $p>0.3$. A similar picture was found with regard to the effects of the two drugs on lever-pressing. Thus, the two doses of haloperidol, but not SCH 23390, reduced the number of ELP-C, $F(3,23)=5.96$, $p<0.005$ (*post hoc* LSD comparisons indicated a significant difference between the vehicle group and the 0.05 and 0.036 mg/kg haloperidol-treated groups only; $p<0.05$), and the number of ELP-U, $F(3,23)=2.78$, $p=0.064$ (*post hoc* LSD comparisons indicated a significant difference between the vehicle group and the 0.05 mg/kg haloperidol-treated group, $p<0.05$, and a nearly significant difference between the vehicle group and the 0.036 mg/kg haloperidol group, $p=0.053$).

DISCUSSION

Administration during the test stage of the D_1 antagonist SCH 23390 at the three doses tested (0.005, 0.01 and 0.03 mg/kg) decreased the number of ELP-U and the number of uncompleted trials, without affecting the number of ELP-C or the number of completed trials (experiment 1). In contrast, the administration of the D_2 antagonist haloperidol dose-dependently decreased the number of ELP-C and ELP-U, as well as the number of completed and

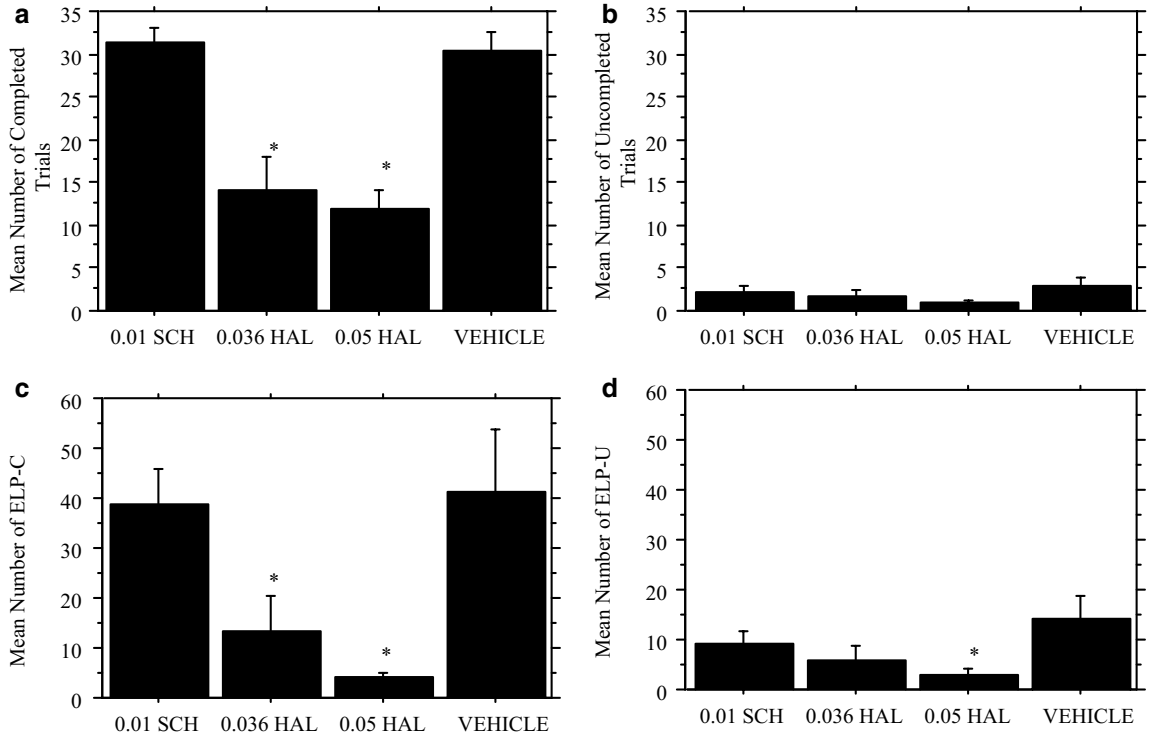

Figure 3 Mean and standard error of the number of (a) completed trials, (b) uncompleted trials, (c) ELP-C and (d) ELP-U on the test day of rats treated with vehicle, 0.01 mg/kg SCH 23390, or 0.036 or 0.05 mg/kg haloperidol in regular extinction.

uncompleted trials (experiments 2 and 3). SCH 23390 at 0.01 mg/kg had no effect on regular extinction, whereas the two doses of haloperidol that decreased lever-pressing in the post-training signal attenuation procedure (0.036 and 0.05 mg/kg) had a similar effect in regular extinction (experiment 4).

The finding that 0.01 mg/kg SCH 23390 reduced ELP-U in post-training signal attenuation but not in regular extinction suggests that the two types of ELP-U are pharmacologically different. We have recently found that lesions to the rat orbital cortex also differentially affected the two types of ELP-U, increasing ELP-U in post-training signal attenuation but not in regular extinction (Joel *et al*, submitted). Although comparisons across experiments may be problematic, an inspection of the behavior of vehicle-treated rats in Figures 1–3 suggests that these rats exhibited a high number of ELP-U when the test stage was preceded by signal attenuation (Figures 1 and 2), but not when it was not (Figure 3). Taken together, these observations suggest that ELP-U induced by signal attenuation are both quantitatively and qualitatively different from ELP-U in regular extinction.

The finding that haloperidol reduced ELP-C and ELP-U in the two procedures (post-training signal attenuation and regular extinction) is consistent with extant findings that this drug has a deleterious effect on lever-pressing (eg Fowler and Liou, 1998; Salamone *et al*, 1996), and with the view that D_2 receptors are involved in motor performance (Beninger and Miller, 1998; Sutton and Beninger, 1999). In contrast to haloperidol, the effects of SCH 23390 at the doses used here were restricted to ELP-U induced by post-training signal attenuation; that is, this drug reduced ELP-U but not ELP-C in the post-training signal attenuation procedure and had no effect on either type of lever-press in regular extinction. The pattern of SCH 23390-induced effects in the two procedures is consistent with our hypothesis that the behavioral response to signal attenuation is mediated via D_1 receptors. It should be noted that the post-training signal attenuation procedure bears some similarity to conditioned reinforcement procedures, which also include an early stage of classical conditioning between a neutral stimulus and an unconditioned stimulus and a test stage in which the conditioned stimulus is presented without the unconditioned stimulus (Mackintosh, 1974), and in which D_1 receptors have been shown to play an important role (Sutton and Beninger, 1999). In our procedure, however, there is an additional stage before the test, the signal attenuation stage, during which the conditioned reinforcer properties of the conditioned stimulus are extinguished by repeatedly presenting it without the primary reinforcement. Compulsive lever-pressing therefore does not seem to be a type of responding for conditioned reinforcement. (For a detailed discussion of the similarities and differences between our procedure and conditioned reinforcement procedures, see Joel and Avisar, 2001; Joel *et al*, 2001).

The mechanisms underlying the involvement of D_1 receptors in the production of compulsive lever-pressing can at present only be speculated on, but some insight may be gained by considering the response of dopaminergic neurons to the presentation of the compound stimulus on trials on which rats exhibit compulsive lever-pressing (ie test preceded by signal attenuation) and on trials on which they do not (ie lever-press training and regular extinction).

The most comprehensive studies of the firing patterns of DA neurons in behaving animals have been conducted by Schultz and colleagues. These authors found that DA neurons respond phasically to primary rewards, but as the experiment progresses, the response of these neurons gradually shifts back in time from the primary reward to reward-predicting stimuli. In addition, when an expected reward is omitted, DA firing is depressed (Schultz, 1998).

Applying these findings to the different types of trials, it may be expected that, at the beginning of lever-press training, stimulus presentation would be accompanied by an increase in DA cell firing, because the stimulus is an unexpected reward-predicting stimulus. By the end of this stage, however, stimulus presentation would no longer be accompanied by a DA response, as the stimulus is predicted. During test trials conducted after signal attenuation, stimulus presentation would be accompanied by a phasic depression of DA cell firing, as occurs when an expected reward is omitted, because the stimulus has lost its rewarding properties at the signal attenuation stage. In contrast, on regular extinction trials, the presentation of the stimulus will have no effect on DA cell firing. Rather, these cells will be phasically depressed after the rat inserts its head into the food magazine and encounters no reward.

The above analysis suggests that a test stage conducted after signal attenuation differs from lever-press training and regular extinction in that only in the former the presentation of the light-tone stimulus is accompanied by a phasic decrease in DA firing. The present finding that compulsive lever-pressing is attenuated by a D_1 antagonist suggests that the phasic decrease in DA levels is signaled by D_1 receptors. Phasic increases in DA levels have been previously suggested to be signaled by D_1 rather than D_2 receptors, based on the fact that most D_1 receptors are in the low-affinity state, the reverse being true for D_2 receptors (Schultz, 1998), as well as on the pattern of the behavioral effects induced by D_1 and D_2 agonists and antagonists (Beninger and Miller, 1998). Since striatal DA levels are reported to increase during lever-pressing for reward (eg Kiyatkin and Gratton, 1994; Richardson and Gratton, 1996), it is possible that the phasic decrease in DA levels, which is hypothesized to underlie compulsive lever-pressing, is also signaled by low-affinity D_1 receptors.

It follows that manipulations that prevent the phasic decrease in D_1 receptor stimulation (eg the administration of a D_1 antagonist or agonist) should be expected to attenuate compulsive lever-pressing, whereas manipulations that increase this factor would increase compulsive lever-pressing. Consistent with the latter is our previous finding that the behavioral response to signal attenuation is increased following termination of repeated administration of SCH 23390 (Joel *et al*, 2001). Since chronic treatment with SCH 23390 leads to an increase in the density of D_1 receptors in the striatum (Creese and Chen, 1985; Giorgi *et al*, 1993; Hess *et al*, 1986, 1988; Lappalainen *et al*, 1992; Memo *et al*, 1987; O'Boyle *et al*, 1993; Porceddu *et al*, 1985), the signaling of a phasic DA decrease is expected to be amplified by the larger number of D_1 receptors, leading to an abnormally high level of compulsive lever-pressing.

Considering the behavioral correlates of the hypothesized DA responses, note that, on the lever-press training and regular extinction trials, the presentation of the stimulus does not lead to a change in DA cell firing and that, at the behavioral level, a lever-press response is followed by a magazine approach. In contrast, the behavioral correlate of the phasic decrease in DA cell firing is lever-presses that are not followed by a magazine approach. It may therefore be suggested that a phasic decrease in DA disrupts the transition from pressing the lever to approaching the food magazine, leading to compulsive lever-pressing. The latter suggestion accords with Saxena *et al*'s (1998) description of compulsive behavior as resulting from 'capture' of the system in a specific behavior because of the inability to switch to another behavior. Moreover, these authors suggested that the inability to switch is a result of an excess 'tone' in a D_1-dependent orbitofrontal-subcortical pathway relative to a D_2-dependent orbitofrontal-subcortical pathway.

The present results are consistent with results obtained with other animal models of OCD that have linked changes in the dopaminergic system to compulsive-like behaviors. Thus, Szechtman and colleagues have found that repeated administration of the D_2 agonist quinpirole induces compulsive checking behavior in rats (Eilam and Szechtman, 1995; Szechtman *et al*, 1998). Campbell *et al* (1999a–c) created a transgenic mouse model of OCD in which the function of D_1 receptor-expressing neurons in cortical and limbic regions is selectively potentiated, leading to a variety of compulsive-like behaviors, including episodes of perseverance of normal behaviors, repetitive leaping and repetitive nonaggressive biting of siblings.

In addition to being consistent with the hypothesis that DA plays an important role in OCD, the present results have some relevance for the treatment of OCD. Thus, the demonstration that compulsive lever-pressing is decreased by a D_2 blocker is consistent with the clinical evidence for the beneficial effects of adding D_2 antagonists to SRIs in the treatment of OCD patients (McDougle *et al*, 1990, 1994; Sasson and Zohar, 1996; Saxena *et al*, 1996). The present finding, however, that haloperidol dose-dependently reduces both compulsive lever-pressing (ELP-U) and noncompulsive lever-pressing (ELP-C) suggests that the beneficial clinical effect of D_2 antagonists may result from a nonspecific effect on behavioral output, rather than from a selective decrease in compulsive behaviors.

The present study suggests that a more selective approach to the treatment of OCD may be the blockade of D_1 receptors. Such a suggestion has been previously made by Saxena *et al* (1998). To the best of our knowledge, there has been only one study that assessed the effects of a drug that blocks the D_1 receptor (among other receptors), namely clozapine, on OCD symptoms. McDougle *et al* (1995) found that chronic treatment with clozapine did not improve obsessions and compulsions in a group of patients refractory to treatment with SRI, SRI and haloperidol, and behavioral treatment. While contradictory to the present suggestion, the results of McDougle *et al*'s study should be treated with caution, because their group of patients was very unusual in its refractoriness to all types of treatment known to date and because coadministration of an SRI may be needed to demonstrate the beneficial effects of a D_1 antagonist, as is the case with D_2 antagonists (McDougle, 1997; McDougle *et al*, 1994).

Alternative means of treating OCD patients derives from our hypothesis that a phasic DA decrease underlies compulsive behavior. Thus, compounds that abolish phasic DA responses or their detection (eg D_1 agonists) may attenuate compulsions. A potential advantage of treatment with D_1 agonists rather than antagonists is that chronic administration of antagonists (but not agonists) may result in exaggeration of symptoms following treatment termination, as a result of treatment-induced increase in the density of D_1 receptors (Creese and Chen, 1985; Giorgi *et al*, 1993; Hess *et al*, 1986, 1988; Lappalainen *et al*, 1992; Memo *et al*, 1987; O'Boyle *et al*, 1993; Porceddu *et al*, 1985). Indeed, repeated administration of SCH 23390 in rats led to an increase in compulsive behavior following the termination of drug administration (Joel *et al*, 2001).

Given that compulsive lever-pressing may provide a rat model of compulsive behavior in OCD patients, the present findings and hypothesis may provide a link between findings implicating abnormalities of the dopaminergic system in the production of obsessions and compulsions in patients and the view that obsessions and compulsions result from a deficient response feedback mechanism. It may be suggested that, in OCD patients, one result of the deficient response feedback mechanism is an abnormal occurrence of a phasic DA decrease following task completion, instead of the normal lack of DA response under such conditions. Such a decrease may disrupt switching to a different behavior, thus resulting in a repeated emission of the same behavior. In addition, because normally a phasic decrease in DA levels occurs when task completion does not yield its expected outcome, pathological occurrences of such a decrease may account for the chronic lack of feeling of task completion reported by OCD patients (Rasmussen and Eisen, 1992).

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