DOPAMINERGIC MODULATION OF RISK-BASED DECISION MAKING

by

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ABSTRACT

Psychopharmacological studies have implicated the mesolimbic dopamine (DA) system in the mediation of cost/benefit evaluations about effort-related costs associated with larger rewards. However, the role of DA in risk-based decision making remains relatively unexplored. The present study investigated how systemic manipulations of DA transmission affect risky choice assessed with a probabilistic discounting task. Over discrete trials, rats between two levers; a press on the "small/certain" lever always delivered one reward pellet, whereas a press on the other, "large/risky" lever delivered four pellets, but the probability of receiving reward decreased across the four trial blocks (100%, 50%, 25%, 12.5%). In separate groups of well-trained rats we assessed the effects of the DA releaser amphetamine, as well as receptor selective agonists and antagonists. Amphetamine consistently increased preference for the large/risky lever; an effect that was blocked or attenuated by co-administration of either D_1 (SCH23390) or D_2 (eticlopride) receptors antagonists. Blockade of either of these receptors alone induced risk aversion. Conversely, stimulation of D_1 (SKF81297) or D_2 (bromocriptine) receptors also increased risky choice. In contrast, activation of D_3 receptors with PD128,907 induced risk aversion. Likewise, D3 antagonism with nafadotride potentiated the amphetamine-induced increase in risky choice. Blockade or stimulation of D_4 receptors did not reliably alter patterns of choice. These findings indicate that DA plays a critical role in mediating risk-based decision making, where increased activation of D_1 and D_2 receptors biases choice towards larger, probabilistic rewards, whereas D_3 receptors appear to exert opposing effects on this form of decision making.

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I INTRODUCTION

Alterations in decision making involving risks and rewards have been observed with a variety of clinical disorders. In particular, individuals with disorders associated with perturbations in the dopamine (DA) system, such as schizophrenia, Parkinson's disease, and chronic amphetamine abuse show impairments on measures of risk-based decision making, such as the Iowa Gambling Task (IGT; Shurman et al., 2005; Mimura et al., 2006) and the Cambridge Gambling Task (Rogers et al., 1999). Likewise, patients with lesions to DA terminal regions, such as the prefrontal cortex, orbitofrontal cortex (OFC) or amygdala make risky, disadvantageous choices on the IGT (Bechara et al., 1999). In keeping with these findings, healthy individuals with temporarily reduced DA levels from consuming a DA-depleting protein beverage are also impaired on the IGT (Sevy et al., 2006).

Interest in how DA may alter risk-based decision making has increased recently in light of numerous clinical reports identifying an association between the use of DA receptor agonists and the emergence of pathological gambling (PG) tendencies in patients with Parkinson's disease (Gallagher et al., 2007), as well as restless legs syndrome (Quickfall and Suchowersky, 2007). The disorder appears to be specific to DA receptor agonist treatment, as these symptoms are not typically observed in patients receiving levodopa monotherapy (Gallagher et al., 2007). The emergence of PG is temporally linked with the onset of DA agonist therapy, and disappears when these treatments are discontinued (Garcia et al., 2007; Imamura et al., 2006), or when taken in conjunction with DA antagonists (Seedat et al., 2000). There is also evidence to suggest that DA functioning is altered in pathological gamblers without neurological disease. Bergh and colleagues (1997) reported both decreased cerebrospinal fluid levels of DA and increased levels of DA metabolites in subjects with PG

relative to controls, indicative of an increase in DA neurotransmission. Furthermore, acute administration of the DA releaser amphetamine to problem gamblers can increase the motivation and desire to gamble (Zack and Poulos, 2004). Other DA medications, such as levodopa, can also alter risk-based decision making in Parkinsonian patients. While patients are "on" medication, they exhibit abnormal betting strategies compared to control subjects (Cools et al., 2003), and have difficulty adjusting their decision strategies after negative outcomes (Frank et al., 2007), but these effects are not observed while patients are "off" medication. Collectively, these studies suggest that increased DA activity may impair risk-based decision making, which then may facilitate the emergence of pathological gambling tendencies.

Further insight into the role of DA in mediating risk/reward decisions comes from neurophysiological recordings of DA neurons in awake, behaving monkeys (Fiorillo et al., 2003). Midbrain DA neurons exhibit a gradual increase in firing rate prior to the potential delivery of a reward with the greatest amount of uncertainty (50%), but display stable activity when the probability of future reward is certain (p = 100% or 0%). These data suggest that DA neurons encode information about reward uncertainty, and that DA release may be greatest under conditions where reward delivery is most uncertain.

Although the above mentioned studies suggest that DA may modulate risk-based decision making, the specific DA receptors involved in this behavior have not been identified. DA agonist medications activate D_2, D_3, and D_4 receptors to varying degrees, but there is some dispute in the literature regarding which subtypes mediate their deleterious effects on decision making. Some have argued that agonists that are more selective for D_3 receptors, such as pramiprexole and ropinirole, are more likely to induce PG (Dodd et al.,

2005; Szarfman et al., 2006), whereas others have reported that mixed D_1/D_2 receptor agonists can also promote PG (Lu et al., 2006). On the other hand, genetic studies have reported increased alterations of the Taq-A1 allele of the D_2 receptor gene (Comings et al., 1996) and the D_4 receptor gene (Pérez de Castro et al., 1997; Comings et al., 2001) in pathological gamblers. Variants of the genes for the D_4 receptor (Benjamin et al., 1996; Li et al., 2006), the D_1 receptor (Comings et al., 1997) and the dopamine transporter (DAT1) (Comings et al., 2001) have also been linked to risky, novelty-seeking, or impulsive-addictive-compulsive behaviors. However, the effects of pharmacological manipulation of these receptors on this form of risk-based decision making have not been explored.

Studies in experimental animals investigating the role of DA in cost/benefit decision making have focused on decisions related to delays or effort requirements to obtain reward. Blockade of DA receptors reduces the preference for rats to either wait longer or work harder to obtain a larger reward (Cardinal et al., 2000; van Gaalen et al., 2006; Denk et al., 2005; Salamone et al., 2001). In contrast, drugs that increase DA transmission, such as amphetamine, can exert differential effects on effort- or delay-based decision making, either increasing or decreasing the preference for larger rewards that come with a greater cost (Floresco et al., 2007). In light of these findings, it is somewhat surprising that there have been very few studies investigating DA modulation of risk-based decision making. In one study, relatively high doses of amphetamine (1-5 mg/kg) induced differential effects on risky choice, although stereotypy typically induced by these doses confounds interpretation of these data (Kaminski and Ator, 2001). Excitotoxic lesions of DA terminal regions, such as the nucleus accumbens core (Cardinal and Howes, 2005) and the OFC (Mobini et al., 2002) induced risk aversion, where lesioned rats were more likely to choose smaller, certain

rewards over large, uncertain ones. However, these studies only provide indirect evidence of the role of DA in this behavior.

To address these issues, we conducted a comprehensive study investigating how manipulations of DA transmission alter risk-based decision making in rats using a probabilistic discounting task (Cardinal and Howes, 2005). We examined the effects of the DA releaser amphetamine, as well as selective antagonists and agonists specific to D_1, D_2, D_3, and D_4 receptors on rats' choice behavior. In addition, we evaluated whether the effects of amphetamine on risky choice could be blocked by co-administration of DA antagonists in order to determine which receptors are mediating the effects of amphetamine.

II MATERIALS AND METHODS

ANIMALS

Four groups of eight male Long Evans rats (Charles River Laboratories, Montreal, Canada) weighing 275-300g at the beginning of behavioral training were used. Upon arrival, rats were given one week to acclimatize to the colony and food restricted to 85%-90% of their free feeding weight starting one week before behavioral training and given ad-libitum access to water for the duration of the experiment. Feeding occurred in the rats' home cages at the end of the experimental day and body weights were monitored daily. All testing was in accordance with the Canadian Council of Animal Care and the Animal Care Committee of the University of British Columbia.

APPARATUS

Behavioral testing was conducted in eight operant chambers (30.5 x 24 x 21cm; Med-Associates, St. Albans, VT., USA) enclosed in sound-attenuating boxes. Individual rats were assigned to one of the chambers for the duration of the study. The boxes were equipped with a fan to provide ventilation and to mask extraneous noise. Each chamber was fitted with two retractable levers, one located on each side of a central food receptacle where food reinforcement (45 mg; Bioserv, Frenchtown, NJ) was delivered via a pellet dispenser. The chambers were illuminated by a single 100-mA house light located in the top-center of the wall opposite the levers. Four infrared photobeams were mounted on the sides of each chamber, and another photobeam was located in the food receptacle. Locomotor activity was indexed by the number of photobeam breaks that occurred during a session. All experimental data were recorded by an IBM personal computer connected to the chambers via an interface.

LEVER PRESS TRAINING

Our initial training protocols were adapted from those of Cardinal et al. (2000). On the day prior to their first exposure to the operant chamber, rats were given approximately 25 food reward pellets in their home cage. On the first day of training, 2-3 pellets were delivered into the food cup and crushed pellet was placed on the active lever before the animal was placed in the chamber to facilitate the learning of the instrumental response. Rats were first trained under a fixed-ratio 1 schedule to a criterion of 60 presses in 30 min, first for one lever, and then repeated for the other lever (counterbalanced left/right between subjects). They were then trained on a simplified version of the full task. These 90 trial sessions began with the levers retracted and the operant chamber in darkness. Every 40 s, a trial was initiated with the illumination of the houselight and the insertion of one of the two levers into the chamber. If the rat failed to respond on the lever within 10 s, the lever was retracted, the chamber darkened and the trial was scored as an omission. If the rat responded within 10 s, the lever retracted and a single pellet was delivered with 50% probability. This procedure was used to familiarize the rats to the probabilistic nature of the full task. In every pair of trials, the left or right lever was presented once, and the order within the pair of trials was random. Rats were trained for approximately 5-6 days to a criterion of 80 or more successful trials (i.e.; $\leq$ 10 omissions).

RISK DISCOUNTING TASK

The task was modified from procedures described by Cardinal and Howes (2005) and is illustrated in Figure 1. Rats received daily sessions consisting of 72 trials, separated into 4 blocks of 18 trials. The entire session took 48 minutes to complete, and the animals were trained 6-7 days per week. A session began in darkness with both levers retracted (the intertrial state). A trial began every 40 s with the illumination of the houselight and insertion

of one or both levers into the chamber (the format of a single trial is shown in Figure 1b). One lever was designated the Large/Risky lever, the other the Small/Certain lever, which remained consistent throughout training (counterbalanced left/right). If the rat did not respond within 10 s of lever presentation, the chamber was reset to the intertrial state until the next trial (omission). When a lever was chosen, both levers retracted. Choice of the Small/Certain lever always delivered one pellet with 100% probability; choice of the Large/Risky lever delivered 4 pellets but with a particular probability (see below). When food was delivered, the houselight remained on for another 4 s after a response was made, after which the chamber reverted back to the intertrial state until the next trial. Multiple pellets were delivered 0.5 s apart. The large reinforcer probability was varied systematically across the session as follows. The 4 blocks were comprised of 8 forced choice trials where only one lever was presented (4 trials for each lever, randomized in pairs) permitting animals to learn the amount of food associated with each lever press and the respective probability of receiving reinforcement over each block. This was followed by 10 free-choice trials, where both levers were presented and the animal had to decide whether to choose the Small/Certain or the Large/Risky lever. The probability of obtaining 4 pellets after pressing the Large/Risky lever varied across the 4 blocks: it was initially 100%, then 50%, 25% and 12.5%, respectively. Rats were trained on the task until as a group, they (1) chose the Large/Risky lever during the first trial block (100% probability) on at least 80% of successful trials, and (2) demonstrated stable baseline levels of choice. Drug tests were administered once the group displayed stable patterns of choice for 3 consecutive days, which was assessed using a procedure similar to that described by Winstanley et al. (2005) and Floresco et al. (2007). In brief, data from three consecutive sessions were analyzed with a repeated-measures ANOVA with two within-subjects factors (Day and Trial Block). If the effect of Block was significant

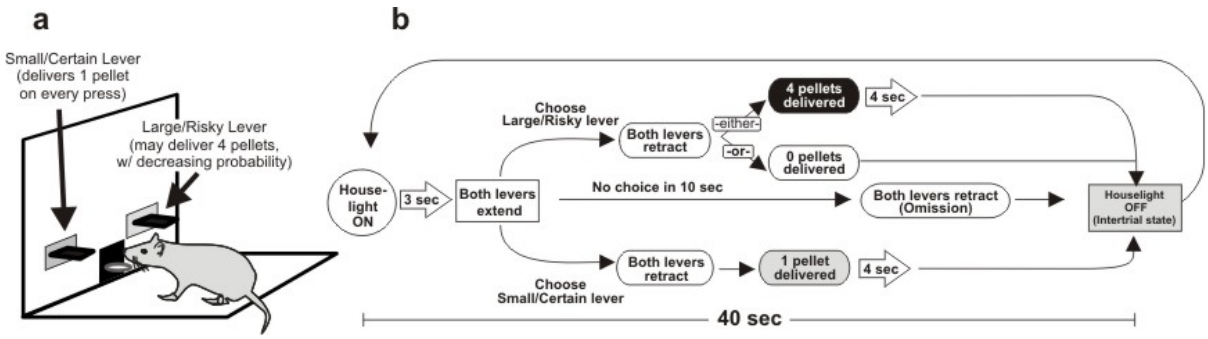

Figure 1. Schematic of the Risk Discounting Task.
(a) Cost/benefit contingencies associated with responding on either the Small/Certain or Large/Risky lever on the Risk Discounting task.
(b) The format of a single free choice trial on the Risk Discounting task.

at the $P<0.05$ level but there was no main effect of Day or Day X Block interaction (at $P>0.1$ level), animals were judged to have achieved stable baseline levels of choice behavior.

SYSTEMIC PHARMACOLOGICAL MANIPULATIONS

We used a within-subjects design for all drug tests. Each test consisted of a two day sequence in which animals received intraperitoneal vehicle (Day 1) and then drug (Day 2) injections 10-40 min prior to a daily training session. These repeated vehicle tests compensated for any drift in baseline levels of choice that may have occurred over training. Following a drug test day, rats were retrained until they again displayed stable patterns of choice, after which subsequent drug tests were administered (approximately another 3-5 days of training). This procedure was repeated until rats in a group had received each of their designated drug treatments.

DRUGS

We used the following drugs in these experiments. DA agonists: d-amphetamine (Sigma-Aldrich, Canada), the D_1 receptor agonist SKF81297 (Tocris Biosciences), the D_2 agonist bromocriptine (Sigma-Aldrich), the D_3 agonist PD128,907 (Tocris Biosciences) and the D_4 agonist PD168,077 (Tocris Biosciences). DA antagonists included: the D_1 antagonist R(+)-SCH23390 hydrochloride (Sigma-Aldrich), the D_2 antagonist eticlopride hydrochloride (Sigma-Aldrich), the D_3 antagonist nafadotride (Tocris Biosciences), and the D_4 antagonist L745,870 (Tocris Biosciences).

All drugs were dissolved in physiological 0.9% saline, sonicated until dissolved, and protected from light, with the exception of bromocriptine and nafadotride, which were first dissolved in dimethyl sulfoxide and then diluted with saline in a 50:50 ratio. The drugs were injected intraperitoneally in a volume of 1 ml/kg bodyweight either 10 min (amphetamine, SKF81297, PD128,907, PD168,077), 20 min (DA antagonists), or 40 min (bromocriptine)

before testing. When drug combinations were tested, the antagonist was administered 20 min before and amphetamine 10 min before testing. Drug tests were separated by at least 3 days.

Drug doses for amphetamine, and the D_1, D_2, and D_4 antagonists were chosen from previous studies, where behaviorally active doses of these drugs were shown to alter prefrontal cognitive functioning, including working memory, and other forms of cost-benefit decision making (van Gaaelen et al., 2006; Cardinal et al., 2000; Zhang et al., 2004; Floresco et al., 2007). In similar dose ranges, these drugs are highly selective for their respective receptor subtype (Hjorth and Carlsson, 1988; Hall et al., 1985; Patel et al., 1997). The D_1 (SKF81297) and D_4 (PD168,077) agonists alter memory performance after systemic administration (Hotte et al., 2005; Browman et al., 2005) and have high selectivity in vivo (Gleason and Witkin, 2006; Bitner et al., 2006). Bromocriptine is 10 and 100 times more potent at D_2 receptors vs D_3 and D_4 receptors, respectively, (Seeman and Van Tol, 1993; Perachon et al., 1999) and is behaviorally active at 5.0 mg/kg (Kelsey and Carlezon, 2002). Nafadotride has approximately 10-20 times greater affinity for D_3 vs D_2 receptors (Griffon et al., 1995) but may only be selective at D_3 receptors at doses under 2.0 mg/kg (Levant and Vansell, 1997). At a 1.0 mg/kg dose, nafadotride alters food-seeking behavior in rats (Duarte et al., 2003). Finally, the D_3 agonist PD128,907 has higher selectivity for D_3 receptors vs D_2 and D_4 receptors (Bristow et al., 1996) and is behaviorally active for D_3 receptors at doses between 0.10 and 0.50 mg/kg (Collins et al., 2005).

The specific pharmacological manipulations that rats in each of the four groups were subjected to are summarized in Table 1. Separate groups of rats were used for experiments using DA antagonists versus the DA receptor agonists. For Group AMPH, the drugs were given in the following order: amphetamine, SCH23390, SCH23390 & amphetamine, eticlopride, and eticlopride & amphetamine. Group D1/4 received three doses each of

SKF81297 and PD168,077. Group D3/4 received L745,870, L745,870 & amphetamine, nafadotride, nafadotride & amphetamine and Group D2/3 received bromocriptine and PD128,907.

BEHAVIORAL MANIPULATIONS

After the animals in Groups D1/4 and D2/3 had completed all drug tests, satiety tests were given to establish the effect of varying primary motivational state on preference for probabilistic reinforcement. Following the last set of drug tests, these groups were retrained until their choice pattern was stable for 3 consecutive days, after which they were given ad-libitum access to lab chow in their home cage for six days. For the combined data from the two groups, the last three days of food restricted behavior (food restriction) was compared to the first day of free feeding (acute free feed), as well as to the last three days of free feeding (long-term free feed).

DATA ANALYSIS

The primary dependent measure of interest was the percentage of choices directed towards the Large/Risky lever for each block of free-choice trials factoring in trial omissions (an index of risky choice). For each block, this was calculated by dividing the number of choices of the Large/Risky lever by the total number of successful trials. For each series of drug tests with amphetamine, the agonists, or the antagonists on their own, the choice data were subjected to separate three-way, repeated-measures ANOVAs with Dose, Test Day (vehicle or drug) and Trial Block as within subject factors. A significant three-way interaction would indicate that the drug manipulation had different effects at the various doses and within a given block. A Dose X Test Day interaction would indicate that the effect of the drug on average choice of the Large/Risky lever across all trial blocks differed depending on the dose. A Test Day X Block interaction would indicate that the effect of the

drug depended on the trial block, but not on the dose. Whenever there was an interaction with or a main effect of Test Day, the drug data was always compared against the vehicle injection that directly preceded it. When amphetamine was combined with each of the antagonists, these choice data were analyzed with two-way, repeated-measures ANOVAs with Test Day (amphetamine, amphetamine + antagonist, or vehicle) and Block as within subject factors. The vehicle used in these analyses was an average of the data for the vehicle associated with the preceding amphetamine drug test and the vehicle associated with the amphetamine + antagonist drug test. A Test Day X Block interaction would indicate that the effect of the drug manipulation compared to vehicle depended on the trial block. With all choice data, the main effect of Block was always significant ($P<0.05$) indicating that rats were discounting as expected (choosing the Large/Risky lever less as the probability of the large reward decreased across the four blocks). Therefore, this effect will not be further mentioned in the results section. The time taken to respond on either lever after insertion into the chamber (response latency) during each trial block was analyzed in a similar manner to choice of the Large/Risky lever for each type of analysis. Locomotor activity (ie., photobeam breaks) and the number of trial omissions were analyzed with one-way repeated-measures ANOVAs, where data from multiple saline tests were averaged. The results of the statistical analyses of these data are only reported when a significant difference was observed. The effects of satiety on behavioral measures were analyzed using two-way, repeated-measures ANOVAs with Day (food restriction, acute free feed, long-term free feed) and Block as within subject factors. A Day X Block interaction would indicate that preference for the Large/Risky lever between the different food manipulations depended on the trial block. Missing values were replaced with the group mean. Appropriate post hoc tests (Dunnett's or Tukey's) were used for pairwise comparisons of significant effects.

III RESULTS

EFFECTS OF INCREASING DA TRANSMISSION WITH AMPHETAMINE ON RISK DISCOUNTING

After 21 days of training, rats in Group AMPH demonstrated sensitivity to decreasing probability of reward, as well as stable choice behavior for 3 consecutive days and subsequently were given the first sequence of drug tests. Over several weeks, rats in Group AMPH received four doses of amphetamine (Table 1). Analysis of the choice data revealed a significant main effect of Test Day ($F(1,7) = 10.68$, $P<0.05$) and a significant Test Day X Block interaction ($F(3,21) = 4.07$, $P<0.05$). The Dose X Test Day X Block interaction only approached statistical significance ($F(9,63) = 1.95$, $P=0.06$), likely because the 0.125 mg/kg dose was not as effective at increasing risky choice on the latter trial blocks. On average, all doses of amphetamine increased choice of the Large/Risky lever compared to saline test days (Dunnett's, $P<0.05$; Figure 2). These increases were significantly higher than saline on the 25% and 12.5% trial block, reflecting a disadvantageous pattern of choice given that choices in these latter blocks should be directed towards the Small/Certain lever in order to maximize reward obtained. Although no dose of amphetamine was significantly more effective than the other doses, the 0.50 mg/kg dose promoted the largest increase in risky choice across the last three blocks and did not significantly increase latencies to respond or trial omissions. Therefore, this dose of amphetamine was used in subsequent drug test combinations with the DA antagonists. The latency to choose between the Large/Risky and Small/Certain levers was only affected by the 1.0 mg/kg dose of amphetamine as indicated by a Dose X Test Day interaction ($F(3,21) = 3.15$, $P<0.05$, Dunnett's, $P<0.05$; Table 2). As expected, locomotor activity was increased by the 0.25, 0.50, and 1.0 mg/kg doses of amphetamine relative to saline ($F(3,21) = 21.56$, $P< 0.001$ and Dunnett's, $P<0.05$; Table 2). The 0.125 mg/kg dose of

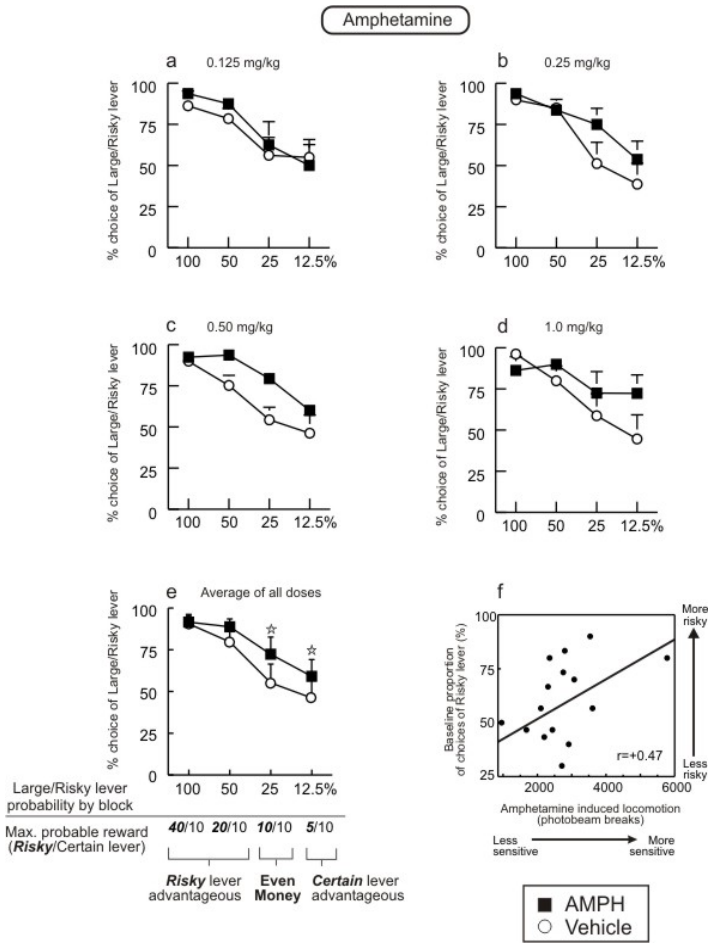

Figure 2. The effects of increased DA transmission with amphetamine on risk-based decision making. Percentage choice for the Large/Risky lever (y axis) is plotted as a function of the Large/Risky lever probability by block (x axis). Symbols represent mean +/- SEM. Asterisks denote significant ($P < 0.05$) differences versus vehicle across all trial blocks. Stars denote significant ($P < 0.05$) differences versus vehicle at a specific block (Test Day x Block interaction). For this figure and all subsequent figures, the vehicle data is an average of all those vehicle tests that were administered immediately prior to the drug tests presented in the particular figure.

(a) For rats in Group AMPH, the 0.125 mg/kg dose of amphetamine did not alter the proportion of choices of the Large/Risky lever.

(b) The 0.25 mg/kg dose significantly increased the proportion of choices of the Large/Risky lever.

(c) The 0.50 mg/kg dose was the most effective dose of amphetamine at increasing risky choice.

(d) The 1.0 mg/kg dose also increased choice of the Large/Risky lever, but increased response latencies.

(e) Comparison of percentage choice of the Large/Risky lever averaged across all vehicle tests compared to the average percentage choice of all amphetamine challenges.

(f) Correlation between baseline preference for the Large/Risky lever and locomotor response following acute administration of the 0.50 mg/kg dose of amphetamine.

amphetamine did not significantly increase locomotion and was also the least effective dose at increasing risky choice. Thus, increasing DA release with amphetamine increases the preference for larger, yet risky rewards.

We were also interested in assessing whether individual differences in baseline risky choice correlated with individual differences in locomotor responses to dopaminergic drugs like amphetamine. Accordingly, we analyzed the data from Groups AMPH, as well as D3/4 (which also received the 0.5 mg/kg dose of amphetamine). We conducted a correlational analysis of baseline choice of the Large/Risky lever averaged over the last three trial blocks with locomotor activity after the first administration of the 0.50 mg/kg dose of amphetamine. We found a significant positive correlation ($r = 0.47$, $P< 0.05$), indicating that higher baseline levels of risky choice were associated with increased locomotor responses to amphetamine (Figure 2f). Thus, rats that were inherently more "risky" in their choice behavior were more sensitive to the locomotor stimulant effects of an acute injection of amphetamine. This suggests a relationship between baseline preference for risky rewards and individual differences in the sensitivity of the DA system.

D_1 RECEPTOR COMPOUNDS

Blockade with SCH23390

Following tests with amphetamine, rats in Group AMPH were retrained until performance was stable and subsequently given two doses of SCH23390 on separate test days (Table 1). This analysis revealed a significant Dose X Test Day X Block interaction ($F(3,21) = 4.27$, $P<0.05$, Dunnett's, $P<0.05$; Figure 3a). The 0.01 mg/kg dose significantly decreased choice of the Large/Risky lever across all trial blocks, including the 100% trial block, indicating a disruption in discriminating between small and large rewards. Yet, the 0.005 mg/kg dose of SCH23390 did not alter discrimination on the 100% trial block, but did

significantly ($P<0.05$) decrease preference for the Large/Risky lever on the 50% and 25% trial blocks compared to saline, indicating that blockade of D_1 receptors induces risk aversion. Treatment with SCH23390 significantly increased the number of trial omissions relative to saline ($F(2,7) = 7.18$, $P<0.01$; Table 2). Analysis of the response latency data revealed a significant main effect of Test Day ($F(1,7) = 37.28$, $P<0.01$; Table 2). Both doses of SCH23390 increased choice latencies, and decreased locomotor counts ($F(2,14) = 7.78$, $P<0.01$; Table 2).

Amphetamine + SCH23390

After receiving challenge doses of SCH23390, rats in Group AMPH received combinations of the 0.01 mg/kg dose of SCH23390 and the 0.50 mg/kg dose of amphetamine. Analysis of the choice data revealed a significant Test Day X Block interaction ($F(6,42) = 2.79$, $P<0.05$, Dunnett's, $P<0.05$; Figure 3b). As was observed previously with this group, amphetamine again increased the proportion of choices of the Large/Risky lever on the last three blocks ($P<0.05$). However, pretreating the animals with SCH23390 abolished this effect. Analysis of the response latency data indicated a Test Day X Block interaction ($F(6,42) = 2.86$, $P<0.05$, $P<0.05$; Table 2). This interaction was attributable to the fact that treatment with SCH23390/amphetamine did not alter latencies during the first two trial blocks, but increased response latencies on the 25% and 12.5% blocks compared to both the 0.50 mg/kg dose of amphetamine, as well as vehicle treatments. Amphetamine also increased response latencies compared to vehicle, but only on the 50% block. In addition to its effects on choice, SCH23390 also blocked the increase in locomotion induced by amphetamine ($F(2,14) = 22.45$, $P<0.01$; Table 2).

We conducted a separate analysis comparing the observed effects of SCH23390/amphetamine to an "expected" discounting curve. This was calculated by

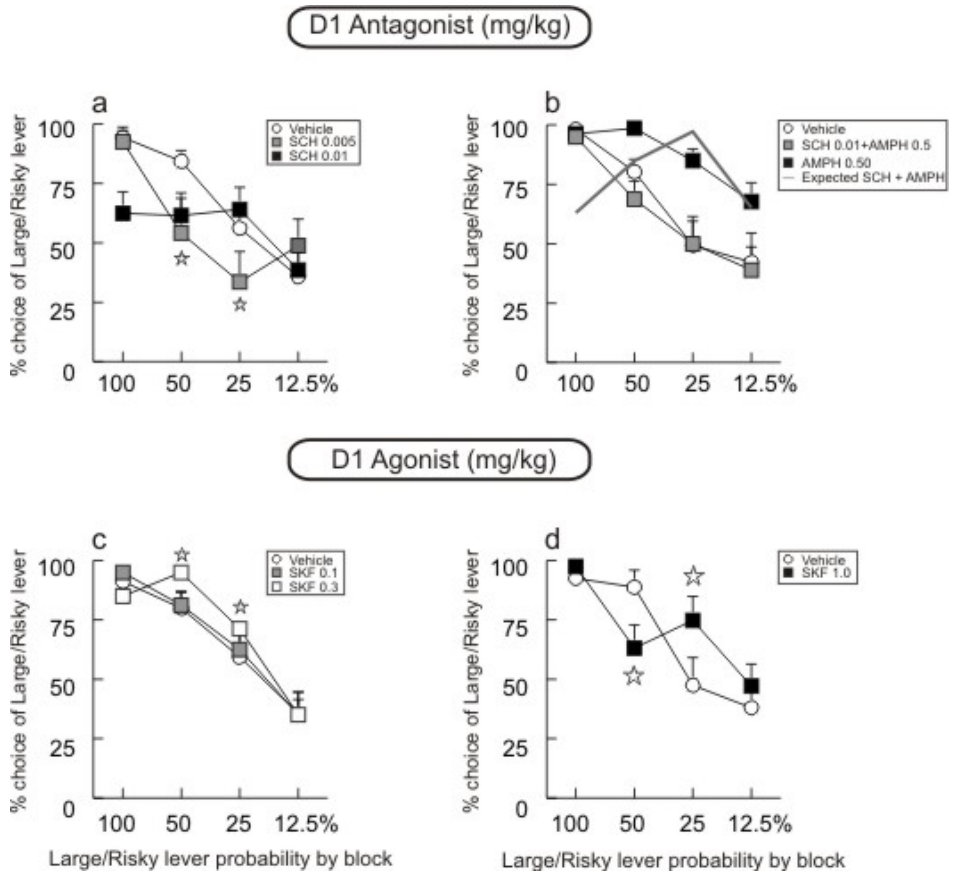

Figure 3. The effects of D_1 receptor manipulations on risk-based decision making. All other conventions are the same as Fig. 2.
(a) D_1 receptor blockade with SCH23390: A high dose of SCH23390 (0.01 mg/kg) disrupted discrimination between small and large rewards, whereas a low dose (0.005 mg/kg) that did not disrupt discrimination decreased the proportion of choices of the Large/Risky lever.
(b) SCH23390 and amphetamine: Blockade of D_1 receptors (0.01 mg/kg) prior to the administration of amphetamine completely blocked the increased proportion of choices of the Large/Risky lever induced by amphetamine alone. The grey line represents an "expected" discounting curve determined by subtracting the effects of SCH23390 from those of amphetamine individually relative to saline injections (i.e., the summed deviation of SCH23390 + amphetamine).
(c) D_1 receptor stimulation with low doses of SKF81297: A low dose (0.1 mg/kg) had no effect, whereas a moderate dose (0.3 mg/kg) increased the proportion of choices of the Large/Risky lever.
(d) D_1 receptor stimulation with a high dose of SKF81297: A high dose (1.0 mg/kg) exerted biphasic effects. Proportion of choices of the Large/Risky lever was decreased during the 50% block and increased on the 25% block.

subtracting the effects of SCH23390 from those of amphetamine individually relative to saline injections. As can be seen in Figure 3b (grey line), the summed deviation of SCH23390 + amphetamine generated a discounting curve that was significantly different from the observed effect of SCH23390/amphetamine ($F(1,7) = 76.97$, $P<0.01$). This suggests that the blockade of the effects of amphetamine on risky choice by SCH23390 are unlikely to be mediated by a simple additive effect of the two drugs (i.e., increased risky choice by amphetamine and risk aversion by SCH23390) cancelling each other out.

Stimulation with SKF81297

Rats in Group D1/4 were trained for 30 days until displaying stable levels of choice and subsequently received three doses of SKF81297. Analysis of the choice data revealed a significant Dose X Test Day X Block interaction ($F(6,42) = 3.76$, $P<0.01$, Dunnett's, $P<0.05$; Figure 3c,d). The 0.1 mg/kg dose of SKF81297 had no effect on choice behavior. The 0.3 mg/kg dose increased risky choice on the 50% and 25% trial blocks compared to saline $P<0.05$), whereas the 1.0 mg/kg dose exerted biphasic effects. On the 50% probability trial block, the 1.0 mg/kg dose significantly decreased risky choice, but on the 25% block, it significantly increased risky choice. Only the 1.0 mg/kg dose of SKF81297 increased trial omissions relative to saline ($F(2,14) = 15.38$, $P<0.01$; Dunnett's, $P<0.05$; Table 2). Analysis of the latency data also revealed a Dose X Test Day X Block interaction ($F(6,42) = 3.42$, $P<0.01$, Dunnett's, $P<0.05$; Table 2) due to the effects of the 1.0 mg/kg dose of SKF81297 increasing response latencies compared to saline during the 100% and 50% trial blocks. Locomotion was also significantly increased by the 1.0 mg/kg dose of SKF81297 ($F(2,14) = 4.48$, $P<0.05$, Dunnett's, $P<0.05$; Table 2). Thus, increasing D_1 receptor activity using a selective agonist increases risky choice, although these effects were not as pronounced as those induced by amphetamine.

D_2 RECEPTOR COMPOUNDS

Blockade with Eticlopride

Following all of the drug tests with SCH23390, rats in Group AMPH were retrained for 9 days and then administered two doses of eticlopride. The analysis revealed a significant main effect of Test Day with no significant interactions ($F(1,7) = 63.76$, $P<0.01$; Figure 4a). On average across the two doses, eticlopride significantly decreased choice of the Large/Risky lever with no differences between the blocks. The 0.03 mg/kg dose of eticlopride significantly increased trial omissions compared to saline ($F(2,14) = 28.89$, $P<0.01$; Table 2) and reduced preference for the Large/Risky lever on the 100% trial block. In contrast, the 0.01 mg/kg dose of eticlopride, which did not significantly increase omissions or alter discrimination, induced risk aversion, and this effect was most prominent over the 50% and 25% blocks. Analysis of the response latency data also revealed a Dose X Test Day X Block interaction ($F(3,21) = 6.24$, $P<0.01$, Dunnett's, $P<0.05$: Table 2) in which the 0.03 mg/kg dose of eticlopride significantly increased response latencies compared to saline during the last three trial blocks, whereas the 0.01 mg/kg had no effect. Both doses of eticlopride also induced a significant decrease in locomotor counts relative to saline ($F(2,14) = 5.37$, $P<0.05$; Table 2).

Amphetamine + Eticlopride

To determine the contribution of D_2 receptors to the effects of amphetamine, we combined the 0.50 mg/kg dose of amphetamine with the 0.01 mg/kg dose of eticlopride. Analysis of the choice data revealed a significant Test Day X Block interaction ($F(6,42) = 2.32$, $P<0.05$, Dunnett's, $P<0.05$; Figure 4b). Amphetamine continued to be effective at increasing risky choice on the latter two trial blocks. The eticlopride/amphetamine combination attenuated the effects of amphetamine on the 25% trial block, though risky

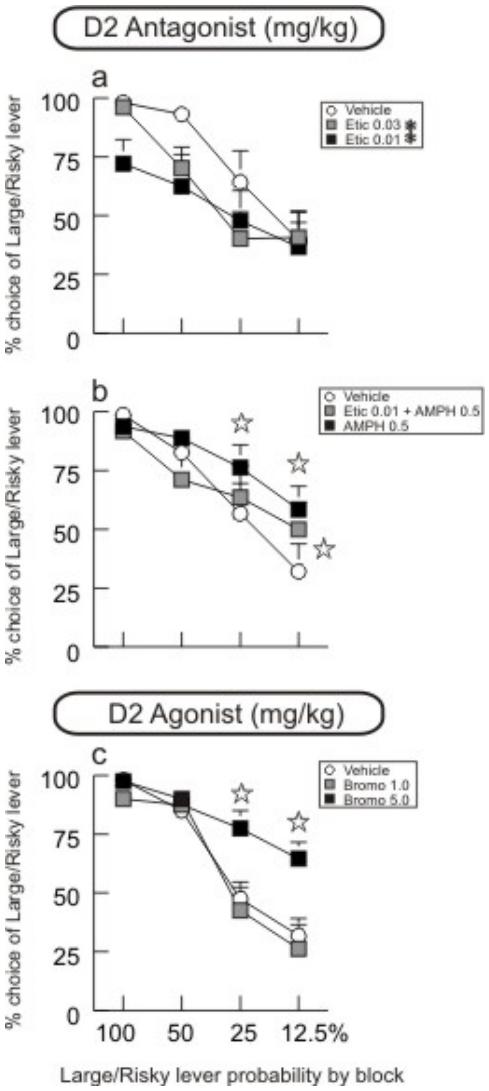

Figure 4. The effects of D_2 receptor manipulations on risk-based decision making. All conventions are the same as Fig. 2.
(a) D_2 receptor blockade with eticlopride: A higher dose of eticlopride (0.03 mg/kg) disrupted discrimination between small and large rewards, whereas a lower dose (0.01 mg/kg) that did not disrupt discrimination decreased the proportion of choices of the Large/Risky lever.
(b) Eticlopride and amphetamine: Blockade of D_2 receptors (0.01 mg/kg) prior to the administration of amphetamine attenuated the increased proportion of choices of the Large/Risky lever induced by amphetamine alone.
(c) D_2 receptor stimulation with bromocriptine: A low dose of bromocriptine (1.0 mg/kg) had no effect, whereas a high dose (5.0 mg/kg) increased the proportion of choices of the Large/Risky lever.

choice was significantly decreased on the 50% block compared to amphetamine and significantly elevated on the 12.5% trial block compared to vehicle. In this case, the drug combination had no significant effects on response latencies (all F's<1.07, NS). The addition of eticlopride also attenuated the increased locomotor effects of amphetamine ($F(2,14) = 30.33$, $P<0.01$; Table 2). Thus, blockade of D_2 receptors attenuated the ability of amphetamine to increase risky choice, but these effects were not as pronounced as those induced by D_1 antagonism.

Stimulation with Bromocriptine

After 20 days of training, rats in Group D2/3 were administered two doses of the D_2 receptor agonist bromocriptine. Analysis of the choice data revealed a significant Dose X Test Day X Block interaction ($F(3,21) = 3.13$, $P< 0.05$, Dunnett's, $P<0.05$; Figure 4c). The 1.0 mg/kg dose of bromocriptine did not significantly alter choice behavior. However, the 5.0 mg/kg dose induced a pronounced increase in risky choice during the 25% and 12.5% trial blocks. The increase in risky choice induced by the 5.0 mg/kg dose was accompanied by an increase in response latencies during the 100%, 25%, and 12.5% trial blocks ($F(3,21) = 4.45$, $P<0.05$, Dunnett's, $P<0.05$; Table 2), as well as locomotor counts ($F(2,14) = 7.36$, $P<0.05$, Dunnett's, $P<0.05$; Table 2). Thus, stimulation of D_2 receptors caused a strong shift in preference towards the larger, yet risky reward.

D_3 RECEPTOR COMPOUNDS

Blockade with Nafadotride

Rats in Group D3/4 were trained for 30 days prior to receiving drug challenge test days. Rats in this group were initially challenged with a D_4 receptor antagonist (see below), after which they were subjected to tests using the D_3 antagonist nafadotride. Blockade of D_3 receptors did tend to increase risky choice at the low and medium doses (i.e., 0.50 and 1.0

mg/kg; Figure 5a), whereas the higher 2.0 mg/kg dose produced a moderate decrease in selection of the Large/Risky lever, possibly due to blockade of D_2 receptors (Levant and Vansell, 1997). However, analysis of the choice data did not reveal a significant Dose X Test Day X Block interaction ($F(6,42) = 0.95$, NS) nor a significant main effect of Test Day ($F(1,7) = 0.16$, NS). Similarly, nafadotride had no effect on response latencies (all F's< 3.04, NS; Table 2). However, the 2.0 mg/kg dose of this compound did cause a significant decrease in locomotor counts ($F(3,21) = 3.10$, $P<0.05$, Dunnett's, $P<0.05$; Table 2).

Amphetamine + Nafadotride

Following challenges with nafadotride, rats in Group D3/4 received injections of the 0.50 mg/kg dose combined with the 0.50 mg/kg dose of amphetamine. Analysis of the choice data produced a significant main effect of Test Day ($F(2,14) = 7.41$, $P<0.01$) and Test Day X Block interaction ($F(6,42) = 5.22$, $P<0.01$, Dunnett's, $P<0.05$; Figure 5b). Amphetamine again biased choice towards the Large/Risky lever. However, the effects of this challenge were not as robust as had been observed previously in these same rats (see below and Figure 6b). Nevertheless, pretreatment with nafadotride actually potentiated the effects of amphetamine on risky choice. Nafadotride/amphetamine significantly ($P<0.05$) increased choice of the Large/Risky lever compared to both vehicle and amphetamine on the 25% and 12.5% trial blocks. The drug combination had no effect on response latencies (all F's< 1.12, NS), but did significantly increase locomotor counts compared to both vehicle and amphetamine tests ($F(2,14) = 21.38$, $P<0.01$, Tukey's, $P<0.05$; Table 2). Thus, blockade of D_3 receptors potentiates the ability of amphetamine to increase both risky choice and locomotor activity.

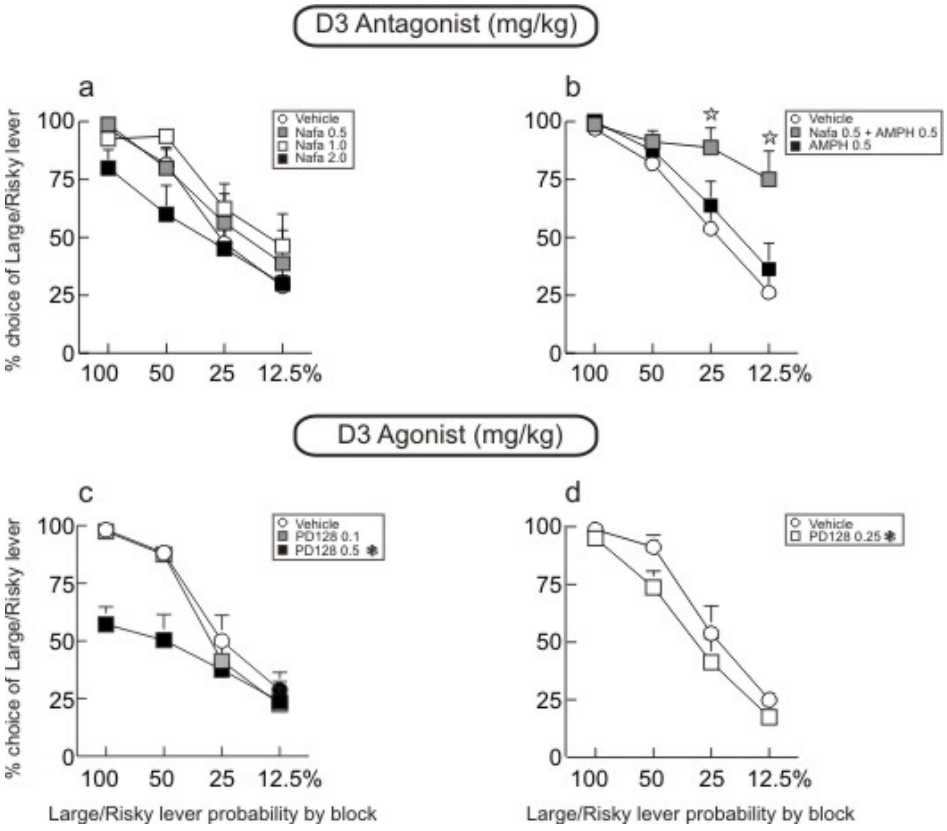

Figure 5. The effects of D_3 receptor manipulations on risk-based decision making. All conventions are the same as Fig. 2.
(a) D_3 receptor blockade with nafadotride: A high dose of nafadotride (2.0 mg/kg) disrupted discrimination between small and large rewards. Low and medium doses (0.50, 1.0 mg/kg) that did not disrupt discrimination moderately increased the proportion of choices of the Large/Risky lever.
(b) Nafadotride and amphetamine: Blockade of D_3 receptors (0.50 mg/kg) prior to the administration of amphetamine potentiated the increased proportion of choices of the Large/Risky lever induced by amphetamine alone.
(c) D_3 receptor stimulation with low and high doses of PD128,907. A low dose (0.10 mg/kg) did not affect choice behavior, whereas a high dose (0.50 mg/kg) disrupted discrimination between small and large rewards.
(d) D_3 receptor stimulation with a medium dose of PD128,907: A medium dose (0.25 mg/kg) decreased the proportion of choices of the Large/Risky lever.

Stimulation with PD128,907

On separate days, rats in Group D2/3 were challenged with three doses of the D_3 agonist PD128,907. Analysis of the choice data revealed a significant Test Day X Dose interaction ($F(2,14) = 7.92$, $P<0.01$, Dunnett's, $P<0.05$; Figure 5c,d). The 0.1 mg/kg dose did not affect choice relative to vehicle treatments. In contrast, the 0.5 mg/kg dose induced a pronounced decrease in the preference for the Large/Risky lever. This effect was apparent during the 100% block, which suggests that this dose of PD128,907 induced a more general disruption in discrimination between different magnitudes of rewards. However, the intermediate dose (0.25 mg/kg) also produced a moderate, but significant ($P<0.05$) decrease in the preference for the Large/Risky lever relative to vehicle treatments. Inspection of Figure 5d reveals that, at this dose, the effects of D_3 receptor stimulation were most prominent during the 50% and 25% blocks, but were not apparent during the 100% block. The 0.50 mg/kg dose significantly increased response latencies ($F(2,14) = 4.58$, $P<0.05$, Dunnett's, $P<0.05$; Table 2). Furthermore, both the 0.25 and 0.5 mg/kg dose induced a moderate decrease in locomotor counts, however, analysis of these data did not achieve statistical significance ($F(3,21) = 2.46$, $P=0.09$; Table 2). Viewed collectively, in contrast to the effects on D_1 and D_2 receptors, activation of D_3 receptors with PD128,907 induces risk aversion, although higher doses of this compound also disrupts discriminations between different magnitudes of rewards.

D_4 RECEPTOR COMPOUNDS

Blockade with L745,870

As noted above, rats in Group D3/4 were administered three doses of the D_4 receptor antagonist L745,870 on separate test days after 30 days of training on the risk discounting task. Analysis of these data revealed that blocking D_4 receptors did not significantly affect

choice using any of the three doses tested, as indicated by the lack of a significant main effect of Test Day ($F(1,7) = 0.39$, NS) or any other interactions (all F's< 3.49, NS), although the Dose X Test Day interaction approached significance ($F(2,14) = 3.49$, $P = 0.059$; Figure 6a). With respect to the response latency data, there was no significant main effect of Test Day ($F(1,7) = 0.04$, NS), nor a three-way interaction ($F(6,42) = 0.47$, NS). Locomotion was also not altered by L745,870 (all F's< 1.72, NS). Thus, blockade of D_4 receptors does not induce a reliable effect on risky choice.

Amphetamine + L745,870

Although blocking D_4 receptors with L745,870 alone did not affect choice, this compound was somewhat effective at attenuating the effects of amphetamine. The analysis of the choice data indicated a significant main effect of Test Day ($F(2,14) = 6.09$, $P<0.05$) and Test Day X Block interaction ($F(6,42) = 2.51$, $P<0.05$, Dunnett's, $P<0.05$; Figure 6b). Amphetamine significantly increased the proportion of choices on the Large/Risky lever on the last three blocks. On the 25% block, the addition of L745,870 attenuated this increased preference for the Large/Risky lever, suggesting that D_4 receptors are involved in the ability of amphetamine to increase risky choice. Response latencies were not affected during this drug test (all F's< 2.83, NS). Furthermore, L745,870 did not alter the increase in locomotor counts induced by amphetamine, as L745,870/amphetamine had significantly higher locomotor counts compared to saline ($F(2,14) = 14.61$, $P<0.01$; Table 2).

Stimulation with PD168,077

Rats in Group D1/4 were also challenged with the D_4 receptor agonist PD168,077 following tests with the D_1 agonists. Analysis of the choice data did not reveal a main effect of Test Day ($F(1,7) = 3.37$, NS) or a Dose X Test Day X Block interaction ($F(6,42) = 1.29$, NS; Figure 6c). Directly stimulating D_4 receptors did not reliably alter preference for the

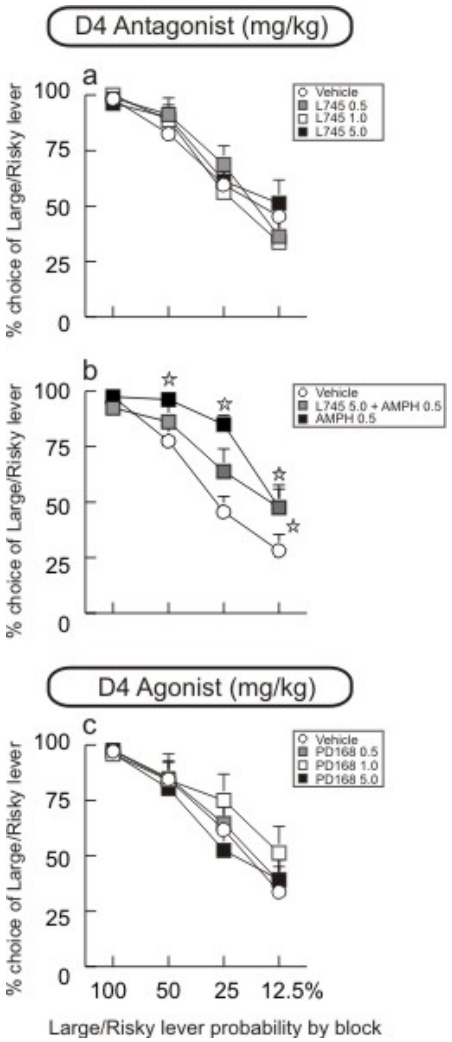

Figure 6. The effects of D_4 receptor manipulations on risk-based decision making. All conventions are the same as Fig.2.
(a) D_4 receptor blockade with L745,870: None of the doses tested reliably affected the proportion of choices of the Large/Risky lever.
(b) L745,870 and amphetamine: Blockade of D_4 receptors (5.0 mg/kg) prior to the administration of amphetamine attenuated the increased proportion of choices of the Large/Risky lever induced by amphetamine alone on the 25% trial block.
(c) D_4 receptor stimulation with PD168,077: None of the doses tested reliably affected the proportion of choices of the Large/Risky lever.

Large/Risky lever in either direction. PD168,077 also did not significantly affect latencies to respond or locomotor counts (all F's< 1.91, NS). Thus, D_4 receptors appear to have a limited role in mediating risky choice.

EFFECTS OF ACUTE AND LONG-TERM FREE FEEDING

Analysis of the choice data revealed a significant Day X Block interaction ($F(6,90) = 6.00$, $P<0.01$, Dunnett's, $P<0.05$; Figure 7). Compared to food restriction, acute and long-term free feeding reduced choice of the Large/Risky lever on the 100% and 50% trial blocks, but increased risky choice on the 12.5% block. Locomotor activity was not altered by an acute increase in free feeding, but long-term free feeding significantly decreased counts compared to food restriction ($F(2,30) = 3.93$, $P<0.05$). In addition, both acute and long-term free feeding significantly increased response latencies during the latter trial blocks ($F(6,90) = 10.09$, $P<0.01$), as well trial omissions ($F(2,30) = 13.55$, $P<0.01$; Table 2) compared to food restriction. Although choices were altered by free feeding, rats still displayed prominent discounting of the Large/Risky lever throughout the session, as the probability of obtaining the larger reward decreased over blocks.

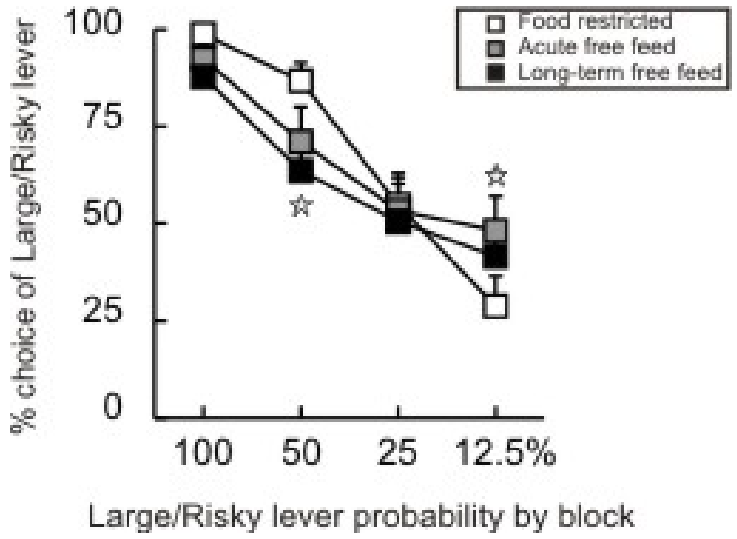

Figure 7. The effects of acute and long-term free feeding on risk-based decision making. Both acute access to food *ad libitum* (gray squares) and long-term free feeding (black squares) decreased the proportion of choices of the Large/Risky lever compared to performance under food restriction conditions (white squares) on the 100% and 50% trial blocks, but increased choice of the Large/Risky lever during the 12.5% trial block.

IV DISCUSSION

Here we report that DA plays a critical role in mediating risk-based decision making, with different receptor subtypes playing opposing roles in the mediation of risky choice. Amphetamine produces a reliable and robust increase in the preference for larger, yet probabilistic rewards, which is either blocked or attenuated by D_1, D_2, or D_4 receptor antagonists. In contrast, pretreatment with a D_3 antagonist potentiates the effects of amphetamine. Conversely, decreasing DA activity with D_1 and D_2 antagonists reduces preference for the Large/Risky lever. Furthermore, administration of receptor selective D_1 or D_2 agonists also increases risky choice, whereas D_3 receptor agonists induce risk aversion. Collectively, these data indicate that increased D_1 or D_2 receptor activity biases choice behavior towards riskier response options associated with larger rewards. In addition, they highlight that D_3 receptor activity appears to promote choice of rewards that are smaller, but more likely to be received.

AMPHETAMINE

To our knowledge, this is the first study to systematically assess the effects of amphetamine on risk-based decision making in experimental animals and demonstrate an increase in risky choice. It is notable that the effects of amphetamine on other forms of cost-benefit decision making have been studied in some detail. For example, doses of amphetamine similar to those used here increase preference for larger, delayed rewards (Cardinal et al., 2000; Wade et al., 2000; van Gaalen et al., 2006). In other instances, these treatments can cause the opposite effects (Evenden and Ryan, 1996; Cardinal et al., 2000). Amphetamine also exerts dose-dependent, biphasic effects on effort discounting, in which low doses increase the tendency for rats to work for a larger reward, whereas higher doses

reduce preference for larger rewards that come with a greater amount of effort (Floresco et al., 2007). In the current study, all doses of amphetamine increased choice of the lever associated with the larger, yet probabilistic reward. In other types of cost/benefit decision making, the increased choice of the high reward/high cost alternative induced by amphetamine is considered advantageous in terms of maximizing reward obtained. However, the optimal strategy in the current task is to limit preference for the Large/Risky reward alternative in the latter trial blocks, and amphetamine administration induces the opposite, disadvantageous pattern of choice by promoting risky choice in these blocks. These findings suggest that psychostimulant drugs like amphetamine can exert differential effects on certain forms of cost/benefit decision making, depending on the particular type of cost animals must evaluate.

The effect of acute administration of amphetamine on risk-based decision making appears to be attributable primarily to alterations in DA transmission, as pretreatment with DA antagonists significantly blunted the risk-promoting effects of amphetamine. In particular, the D_1 antagonist completely blocked the ability of amphetamine to increase risky choice, while D_2 and D_4 antagonists significantly attenuated the effects of amphetamine. Although direct disruptions of serotonergic functioning do not seem to disrupt probabilistic discounting (Mobini et al., 2000), the possibility that interactions between dopaminergic, serotonergic and noradrenergic systems underlie amphetamine-induced increases in risky choice cannot be completely ruled out. Interestingly, our observation that increasing DA transmission with amphetamine increased risky choice is consistent with the behavior of chronic amphetamine abusers, who not only make inappropriate choices in real-life, but also in tasks measuring risk-related decision making (Rogers et al., 1999).

In a previous study, Kaminski and Ator (2001) reported that amphetamine increased preference for a larger, probabilistic reinforcer; however the increase only occurred in two rats whose baseline choice of the probabilistic lever was low (i.e., 20%). Rats whose baseline choice of the probabilistic lever was considered high (> 50%) actually decreased their preference for the risky lever (n=4) after an amphetamine challenge. The effects also depended on the intertrial interval length. Despite a small sample, these data suggest that there may be individual differences in baseline patterns of risky choice, which may contribute to different behavioral responses to dopaminergic drugs like amphetamine. Note that in the present study, there was individual variability in baseline risky choice, but amphetamine increased preference for the Large/Risky lever in all rats of each group tested. Indeed, we observed a positive correlation between baseline levels of risky choice and sensitivity to the locomotor effects of amphetamine (Figure 2f), suggesting that animals who are normally "risky" may have a predisposed sensitivity to changes in DA transmission.

D_1 AND D_2 RECEPTORS PROMOTE RISKY CHOICE

As opposed to the effects of amphetamine, blocking D_1 or D_2 receptors, at doses that did not disrupt reward sensitivity, induced risk aversion. Conversely, selective activation of these receptors increased risky choice. We also observed biphasic effects with the 1.0 mg/kg dose of SKF81297, such that rats were risk averse when the probability of the Large/Risky lever was 50% and risk prone when the probability was 25%. These effects are particularly interesting given the vast literature on the effects of D_1 receptor stimulation and other types of cognition. D_1 receptor modulation of cognition often takes the form of an "inverted U-shaped" function, where either reductions or increases in D_1 receptor activity can impair cognitive abilities, such as working memory (Arnsten 1997; Williams and Castner, 2006; Zahrt et al., 1997; Floresco and Phillips, 2001; Floresco and Magyar, 2006; Chudasama and

Robbins, 2004). In the present study, the high dose of the D_1 agonist promoted a risk averse pattern of choice when the probability of the large reward was the most uncertain (i.e., 50% block). This is notable given that DA neurons display the greatest firing rate when the probability of reward is the most uncertain (ie., 50%; Fiorillo et al., 2003). Therefore, it is plausible that endogenous DA activity may peak during those particular trials so that additional stimulation of D_1 receptors may then impair decision making by overactivating the DA system. Although D_1 receptor activity plays more of a role in the risk-promoting effects of amphetamine compared to D_2 receptors, D_2 stimulation with bromocriptine induced a substantially greater increase in risky choice. This is particularly intriguing given that bromocriptine is one of the original DA agonists used to treat Parkinson's disease and has been linked to cases of agonist-induced pathological gambling, as have other D_2 agonists (Gallagher et al., 2007). In contrast to these effects, D_4 receptor agents did not reliably affect choice. While the D_4 receptor gene has been linked to ADHD (Li et al., 2006), indices of novelty seeking (Benjamin et al., 1996), as well as pathological gambling (Pérez de Castro et al., 1997), our data do not suggest a role for the D_4 receptor in risk-based decision making. Blocking or directly stimulating D_4 receptors did not affect basal levels of choice. However, pretreatment with L745,870 attenuated the amphetamine-induced increase in risky choice, suggesting that D_4 receptors may play a permissive role in mediating the effects of amphetamine.

OPPOSING ROLES OF D_2 VERSUS D_3 RECEPTORS ON RISK-BASED DECISION MAKING

Compared to the effects of D_2 receptor stimulation, the D_3-preferring agonist PD128,907, exerted the opposite effects on risky choice. Directly stimulating D_3 receptors, with doses that did not alter reward sensitivity, *decreased* preference for the Large/Risky lever, whereas

D_2 receptor stimulation had the opposite effect in the same animals. Higher doses of D_3 agonists have been shown to inhibit endogenous DA release (Gobert et al., 1996) and DA neuron firing (Millan et al., 2000), which would reduce activity at D_1 and D_2 receptors. In addition, co-administration of the D_3 antagonist, nafadotride, with amphetamine potentiated the increase in risky choice induced by amphetamine alone, further supporting the notion that D_3 receptors work in opposition to D_1 and D_2 receptors on risk-based decision making. These results complement an emerging literature demonstrating opposing roles for D_3 vs D_2 or D_1 receptors in delay discounting (van den Bergh et al., 2006; van Gaalen et al., 2006), memory consolidation (Sigala et al., 1997), yawning behaviour (Collins et al., 2005) and locomotion (Millan et al., 2004). In the current study, we also saw opposing effects of D_2 and D_3 agonists on locomotion, with bromocriptine increasing locomotor counts, whereas PD128,907 decreased locomotion. It is interesting to point out that our findings showing a D_3 agonist induces risk aversion is contrary to the notion that D_3-preferring agonists are the culprits behind DA agonist-induced pathological gambling, due to the greater incidence of pathological gambling in patients taking pramipexole (Dodd et al., 2005; Szarfman et al., 2006). Our evidence supports the notion that agonists stimulating D_2 receptors are more likely to induce risky choice or gambling. Together, this trend suggests that D_3 receptors appear to be functioning to promote risk aversion, in contrast to D_2 receptors, which promote risky choice.

FREE FEEDING

Our satiety manipulations were particularly revealing. Both acute and long-term free feeding produced similar results: animals were risk averse on the first two blocks, similar to food-restriction on the third block, and risk prone on the last block (Figure 7). This particular pattern of choice was actually the most disadvantageous strategy to gain the most reward,

indicating that motivation plays an important role in risk-based decision making. Furthermore, the fact that this pattern was also not characteristic of any drug administration indicates that these effects were not mediated by primary motivational factors related to reward, but may be critical for assessing the probability of different reward outcomes in order to make the most optimal choice. This is in keeping with the notion that although rats are choosing among natural, consumable rewards (i.e., sugar pellet reward), as opposed to monetary reward typically used in human research studies, recent evidence suggests that probabilistic discounting shows a similar pattern, regardless of whether the reward earned is consumable or nonconsumable (Estle, Green, Myerson, and Holt, 2007).

MECHANISMS UNDERLYING CHANGES IN RISKY CHOICE INDUCED BY DA MANIPULATIONS

It could be argued that the increase in risky choice induced by increased DA activity was due to animals fixating on the alternative associated with the larger reward or an impairment in perceiving reward magnitude. Changing the magnitude of reinforcers has been shown to affect choice behavior using probabilistic rewards (Mazur, 1988). In our task, the difference between 1 and 4 sugar pellets may have been perceived to be larger or smaller than what actually occurred. If, instead of normally assigning 1 to the small reinforcer and 4 to the large reinforcer, increasing DA activity (e.g. via amphetamine) caused rats to assign values of 1 and 5 or 6 to those same reinforcers respectively, we would expect rats to choose the Large/Risky lever more often (i.e., risk prone) in the latter trial blocks, which is what we observed. However, we find these to be unlikely explanations because in other cost/benefit decision making tasks, similar doses of amphetamine (i.e., 0.5 mg/kg) actually decrease preference for the large reward alternative (Evenden and Ryan, 1996; Floresco et al., 2007). Amphetamine can also have differential effects on preference for a high reward reinforcer

with an associated response cost depending on whether there is a cue present to signal changing delays (Cardinal et al., 2000). In addition, similar doses of amphetamine to those used in the current study have been shown to increase response or task switching on other behavioral paradigms (Evenden and Robbins, 1985; Weiner, 1990). For these reasons, it is unlikely that amphetamine caused perseveration on the Large/Risky lever in the current task. Furthermore, if amphetamine acted to increase the difference in reward magnitude between the two alternatives (and thus, the salience of the high reward alternative), we would expect to see the same increase in preference for the high reward under these different decision making conditions, which is not the case. It is also unlikely that the risk-aversive effects (e.g. D_1, D_2 antagonists, D_3 agonist) induced by our pharmacological manipulations were attributable to alterations in perceived reward magnitude, because lower doses of these drugs only decreased preference for the Large/Risky lever during trial blocks that involved risk (i.e., not on the 100% probability block). In addition, DA depletion of the accumbens does not affect the ability to discriminate between large and small rewards (Salamone et al., 2001), and systemic DA antagonists do not seem to alter perceived quantity of food using a psychophysical procedure (Martin-Iverson et al., 1987). Collectively, these studies suggest that alterations in choice behavior following administration of dopaminergic drugs do not seem to be accounted for by disruptions in cognitive flexibility or perception of reward magnitude.

It has been previously suggested that the underlying process of discounting choice of larger rewards with increasing response costs may be the same for delay and risk/probabilistic discounting (Rachlin et al., 1991; Green and Myerson, 2004; Mazur, 1997; Ostaszewski and Karzel, 2002; Richards et al., 1999). In the present study, reward omission results in a greater overall delay before receiving reward on a subsequent trial. Therefore,

alterations in choice on the risk discounting task used here as a result of dopaminergic drugs could be interpreted as affecting the rats' tolerance to wait for a large reward, rather than to gamble on a risky, large reward. Indeed, alterations in DA transmission alter delay-based decision making (Cardinal et al., 2000; Evenden and Ryan, 1996; Floresco et al., 2007; Wade et al., 2000; van Gaalen et al., 2006). However, increasing evidence from both human and animal studies suggests that these types of decisions may, in fact, be dissociable. In a drug free state, rats differentially alter their preference for large rewards associated with increasing delays or risk when the optimal strategy is to always pick the large reward (Adriani and Laviola, 2006). After extended training, rats will become impulsive and shift to picking the small, immediate reward versus the large, delayed reward as the length of the delay increases (despite receiving less food), but will continue to pick a large, probabilistic reward even when the probability becomes very small. Interestingly, this effect was maintained even when the delay to reward was similar in both tasks (i.e., 60s for large reward). These effects may be related to how much control the animal has over waiting for reward. A situation in which the animal chooses to potentially wait for an unpredictable, large reward may be more appealing than a situation where they always have to wait a guaranteed delay. The fact that rats seem to prefer "binge reinforcement" suggests that this task preferentially promotes patterns of choice resembling gambling rather than impulsivity (Adriani and Laviola, 2006). In clinical populations, a double dissociation has been identified between drug addicts and gamblers with respect to these types of decision making. Drug addicts typically only show abnormal delay discounting, in that they are more impulsive than controls (Bickel et al., 1999; Vuchinich et al., 1997*),* while problem gamblers take bigger risks than controls, but are not impaired at delay discounting (Holt et al. 2003). Discounting of delayed and probabilistic rewards in these gamblers was positively correlated, rather than negatively correlated, as

would be expected if individuals who were classically impulsive, also liked to gamble more. It has also been shown that an individual's tendency to make rapid, impulsive choices and their tendency to bet large amounts of money on uncertain outcomes are independent of each other (Deakin et al. 2004). As well, currency inflation seems to only affect decision making about probabilistic financial rewards, not delayed rewards (Ostaszewski et al., 1998).

Further evidence for dissociable mechanisms underlying delay- versus risk-based decision making comes from neurochemical studies. Amphetamine differentially affects both tasks with regard to advantageous outcomes. Similar doses of amphetamine make rats less impulsive (advantageous; Cardinal et al., 2000; Floresco et al., 2007; Wade et al., 2000; van Gaalen et al., 2006), whereas it increases risky choice observed here (which is disadvantageous), although similar treatments can also increase impulsive choice (Evenden and Ryan, 1996; Cardinal et al., 2000). Notably, the D_2 antagonist eticlopride decreased risky choice in the present study, but similar doses of this drug did not affect delay discounting (van Gaalen et al., 2006). Furthermore, lesions of the 5-HTergic pathway in rats induce impulsivity on a delay discounting task but have no effect on probabilistic discounting (Mobini et al., 2000). Collectively, these studies suggest that impulsivity, as measured by an intolerance to wait for large rewards, and the tendency to make risky choices, are separable processes whose underlying mechanisms can be studied independently.

Given that alterations in DA activity do not seem to increase perseveration in choosing a large reward or alter perceived magnitude of reinforcers, the effects of these manipulations may be more specific to calculating the probability of receiving reward. In the first trial block, animals correctly choose between a certain, small reinforcer and a certain, large reinforcer; however, when the large reinforcer becomes uncertain (latter 3 trial blocks), increasing or decreasing DA activity severely disrupts the animal's ability to make the

optimal choice. In line with what Cardinal and Howes (2005) observed, systemically decreasing D_1 or D_2 receptor activity in our study induced rats to behave as if the probability of an uncertain, large reward was less likely than it really was, thus increasing choice of the certain, small reward. Furthermore, increasing DA activity may have biased choice behavior under the assumption that the probability of the large reward was more likely than it really was. Therefore, increases or decreases in DA transmission may hamper calculations about the relative risks associated a particular choice, resulting in an over- or underestimation of the likelihood of obtaining rewards delivered in a probabilistic manner. The suggestion that DA functions to aid calculations about reward probability is supported by the finding that DA neurons in the VTA have differential activation patterns depending on reward probabilities, with the greatest firing rate occurring when reward probability is most uncertain (Fiorillo et al., 2003). This complements findings that midbrain DA neural activity is increased when a cue is presented that is associated with an unexpected or greater than expected reward (Schultz and Dickinson 2000; Schultz 2006). Midbrain DA neurons also respond to errors in prediction, suggesting that DA activity may contribute to a "teaching signal" about recent errors in predicting reward, and thus, aid the animal in learning the probability of future reward through a trial-by-error process (Schultz and Dickinson, 2000). In our task, DA may function to update the representation of reward probability within each trial block. It has been suggested that DA activity may play a reactive or opportunistic role in adapting baseline decision making processes to the current needs of the organism by bridging internal physiological and psychological states (e.g. hunger, sexual arousal, stress) with executive processes (Phillips et al., 2007). When an animal is faced with food deprivation in its environment, changes in either tonic or phasic DA transmission could help the animal decide whether to take the risk to obtain food in a dangerous situation.

SUMMARY AND CONCLUSIONS

This is the first systematic and comprehensive study of the effects of alterations in DA transmission on risk-based decision making. We have shown that this behavior is remarkably sensitive to increasing DA release, as well as blockade and activation of specific DA receptors. D_1 and D_2 receptors mediate increases in risky choice, both on their own, as well as via the effects of amphetamine. D_3 receptors promote risk aversion and may function to partially inhibit increased risky choice induced by amphetamine. These results provide the groundwork for future studies examining the neural basis of risk-based decision making, as identifying the receptors that mediate risk-based decisions helps elucidate the specific neural circuits that may be underlying this behavior. The present findings also provide a greater understanding of how alterations in DA functioning, either inherent or induced by therapeutic and recreational drugs, can lead individuals to make increased risky choices.

Table 1 Experiments Performed

Group	Manipulation (dose, order administered)
AMPH	d-amphetamine (0.50, 0.25, 0.125, 1.0 mg/kg) SCH23390 (0.01, 0.005 mg/kg) SCH23390 (0.01 mg/kg) + amphetamine (0.50 mg/kg) Eticlopride (0.03, 0.01 mg/kg) Eticlopride (0.01 mg/kg) + amphetamine (0.50 mg/kg)
D1/4	SKF81297 (0.30, 0.10, 1.0 mg/kg) PD168,077 (1.0, 5.0, 0.50 mg/kg) Acute free feeding Long-term free feeding
D3/4	L745,870 (5.0, 1.0, 0.50 mg/kg) L745,870 (5.0 mg/kg) + amphetamine (0.50 mg/kg) Nafadotride (2.0, 1.0, 0.5 mg/kg) Nafadotride (0.50 mg/kg) + amphetamine (0.50 mg/kg)
D2/3	Bromocriptine (5.0, 1.0 mg/kg) PD128,907 (0.10, 0.50, 0.25 mg/kg) Acute free feeding Long-term free feeding

Table 2 Response Latency, Locomotion, Trial Omissions

* denotes $p<0.05$ vs vehicle or control

Drug Test	Latency (sec)	Locomotion counts	Omissions
d-amphetamine (AMPH)			
vehicle	0.54 +/- 0.03	1683 +/- 202	
0.125 mg/kg	0.50 +/- 0.03	1768 +/- 60	
0.25 mg/kg	0.42 +/- 0.01	2387 +/- 289*	
0.50 mg/kg	0.75 +/- 0.03	2675 +/- 212*	
1.0 mg/kg	1.07 +/- 0.05*	3045 +/- 235*	
SCH23390			
vehicle	0.77 +/- 0.09	1297 +/- 230	0.7 +/- 0.4
0.01 mg/kg	1.34 +/- 0.13*	652 +/- 60*	21 +/- 5*
0.005 mg/kg	1.66 +/- 0.29*	670 +/- 90*	17 +/- 6*
SCH23390 + AMPH			
vehicle	0.71 +/- 0.07	1505 +/- 221	
AMPH 0.50 mg/kg	0.99 +/- 0.08*	2943 +/- 184*	
SCH 0.01 mg/kg + AMPH 0.50 mg/kg	1.14 +/- 0.17*	1568 +/- 297	
SKF81297			
vehicle	0.65 +/- 0.03	1316 +/- 164	0.6 +/- 0.4
0.10 mg/kg	0.69 +/- 0.06	1294 +/- 140	0.4 +/- 0.3
0.30 mg/kg	0.78 +/- 0.03	1463 +/- 124	0.3 +/- 0.3
1.0 mg/kg	1.65 +/- 0.49*	1987 +/- 252*	17 +/- 4*
Eticlopride			
vehicle	0.82 +/- 0.12	1237 +/- 233	1 +/- 0.8
0.03 mg/kg	2.65 +/- 0.45*	666 +/- 52*	33 +/- 5*
0.01 mg/kg	1.01 +/- 0.08	979 +/- 216*	6 +/- 4
Eticlopride + AMPH			
vehicle	0.64 +/- 0.04	1078 +/- 197	
AMPH 0.50 mg/kg	0.75 +/- 0.06	2674 +/- 227*	
etic 0.01 mg/kg + AMPH 0.50 mg/kg	0.74 +/- 0.06	1916 +/- 366*	

Table 2 Response Latency, Locomotion, Trial Omissions

* denotes $p<0.05$ vs vehicle or control

Bromocriptine			
vehicle	0.44 +/- 0.03	1299 +/- 236	
1.0 mg/kg	0.37 +/- 0.01	1099 +/- 217	
5.0 mg/kg	0.68 +/- 0.05*	1826 +/- 305*	
Nafadotride			
vehicle	0.49 +/- 0.02	1773 +/- 179	
0.50 mg/kg	0.43 +/- 0.03	1750 +/- 225	
1.0 mg/kg	0.46 +/- 0.02	1530 +/- 203	
2.0 mg/kg	0.48 +/- 0.03	1385 +/- 150*	
Nafadotride + AMPH			
vehicle	0.49 +/- 0.02	1687 +/- 245	
AMPH 0.50 mg/kg	0.43 +/- 0.00	2991 +/- 534	
nafa 0.5 mg/kg + AMPH 0.50 mg/kg	0.48 +/- 0.01	3562 +/- 465*	
PD128,907			
vehicle	0.42 +/- 0.02	1371 +/- 235	
0.10 mg/kg	0.42 +/- 0.01	1249 +/- 244	
0.25 mg/kg	0.52 +/- 0.01	1077 +/- 196	
0.50 mg/kg	1.15 +/- 0.16*	1119 +/- 190	
L745,870			
vehicle	0.48 +/- 0.04	1700 +/- 244	
0.50 mg/kg	0.42 +/- 0.02	1681 +/- 260	
1.0 mg/kg	0.45 +/- 0.04	1742 +/- 248	
5.0 mg/kg	0.53 +/- 0.04	1671 +/- 319	
L745,870 + AMPH			
vehicle	0.49 +/- 0.03	1777 +/- 216	
AMPH 0.50 mg/kg	0.46 +/- 0.01	3091 +/- 491	
L745 5.0 mg/kg + AMPH 0.50 mg/kg	0.54 +/- 0.02	3085 +/- 427*	
PD168,077			
vehicle (sal)	0.74 +/- 0.06	1143 +/- 131	
0.5 mg/kg	0.50 +/- 0.06	1173 +/- 110	
1.0 mg/kg	0.44 +/- 0.13	1042 +/- 152	
5.0 mg/kg	0.49 +/- 0.07	1116 +/- 96	
Food restriction (control)	0.61 +/- 0.04	1254 +/- 102	0.7 +/- 0.3
Acute free feeding	1.27 +/- 0.25*	1136 +/- 95	5 +/- 2*
Long-term free feeding	1.53 +/- 0.20*	1072 +/- 46*	9 +/- 2*

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