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Effects of acute and chronic treatments with dopamine D_2 and D_3 receptor ligands on cocaine vs. food choice in rats

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ABSTRACT

Dopamine D_3 receptor ligands are potential medications for psychostimulant addiction. Medication assessment may benefit from preclinical studies that evaluate chronic medication effects on choice between an abused drug and an alternative, non-drug reinforcer. This study compared acute and chronic effects of dopamine D_2- and D_3-preferring ligands on choice between intravenous cocaine and palatable food in rats. Under baseline conditions, cocaine maintained dose-dependent increases in cocaine choice and reciprocal decreases in food choice. Acutely, the D_2 agonist NPA and antagonist L-741,626 produced leftward and rightward shifts in cocaine dose-effect curves, respectively, while the partial agonist terguride had no effect. All three drugs dose-dependently decreased food-maintained responding. Chronically, NPA and L-741,626 effects on cocaine self-administration showed marked tolerance, while suppression of food-reinforced behavior persisted. Acute effects of the D_3 ligands were less systematic and most consistent with nonselective decreases in cocaine- and food-maintained responding. Chronically, the D_3 agonist PF-592,379 increased cocaine choice, whereas an intermediate dose of the D_3 antagonist PG01037 produced a therapeutically desirable decrease in cocaine choice early in treatment; however, tolerance developed to this effect, and lower and higher doses were ineffective. D_3 ligands failed to significantly modify total cocaine intake, but caused persistent decreases in food intake. Thus, D_2-and D_3-preferring ligands showed distinct profiles, consistent with different pharmacological actions. Additionally, these results highlight the role of acute versus chronic treatment as a determinant of test drug effects. With the possible exception of the D_3 antagonist PG01037, no ligand was promising in terms of cocaine addiction treatment.

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INTRODUCTION

Substance use disorders have become a problem of epidemic proportions in the US and worldwide. Cocaine remains one of the most widely used illegal substances, and despite decades of research, there is no approved medication to treat addiction to cocaine (O'Connor et al., 2014; Skolnick et al., 2015; Czoty et al., 2016). Ligands acting at receptors of the dopamine D_2 family (D_2/D_3/D_4) modulate cocaine self-administration behavior in laboratory animals: agonists produce leftward shifts of the cocaine dose-effect function, while antagonists produce rightward shifts consistent with surmountable antagonism (Bergman et al., 1990; Caine et al., 1999; Barrett et al., 2004). As medication strategies, D_2-preferring or non-subtype selective D_2-family antagonists were not promising, largely because of adverse effects limiting the use of effective doses, and because "anti-cocaine" effects observed with acute administration eroded when given chronically (see Discussion). The D_3 subtype attracted attention as a potential target for treating psychostimulant addiction, due to its restricted localization and high concentration in parts of the mesolimbic reward pathway, its high affinity for dopamine, and the differential alteration of D_2 vs. D_3 receptor availability as a consequence of psychostimulant use (for review see Heidbreder and Newman, 2010; Keck et al., 2015; Sokoloff and Le Foll, 2016). Specifically, post-mortem and PET studies suggest that at least some psychostimulant users, especially heavy users, have elevated D_3 receptor availability and decreased D_2 receptor availability relative to controls (Staley and Mash, 1996; Segal et al., 1997; Boileau et al., 2012; but see Meador-Woodruff et al., 1995). In rats and monkeys, long-term cocaine exposure was shown to increase D_3 receptor availability, decrease D_2 receptor availability, and/or decrease D_2/D_3 ratios (Le Foll et al., 2002; Neisewander et al., 2004; Collins et al., 2011; Nader et al., 2006). Unlike D_2 receptor antagonists, D_3 receptor antagonists administered acutely do not decrease cocaine self-administration under experimental conditions in which cocaine is available at relatively low cost (e.g., low response requirement, no competing reinforcers), but they can decrease cocaine taking under higher cost conditions, although selectivity over reduction in food-reinforced responding was often moderate (Heidbreder and Newman, 2010; Sokoloff and Le Foll, 2016).

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Critical review of laboratory animal evaluations of candidate medications strongly support the notion that predictive validity is dependent upon the inclusion of chronic dosing regimens, whereas acute-only results have often been misleading (Haney and Spealman, 2008; Czoty et al., 2016; see specific examples in the Discussion section). Further, effects on cocaine self-administration (i.e., direct reinforcing effects of cocaine) have predicted clinical efficacy better than modulation of subjective or conditioned effects alone (Comer et al., 2008; Haney and Spealman, 2008). One type of self-administration assay, choice procedures, is gaining popularity, with various proposed advantages over single-reinforcer assays (Banks et al., 2015a; Banks and Negus, 2016). Choice procedures allow behavior allocation to be assessed independently of rates of responding, and the simultaneous evaluation of effects on cocaine and food intake. Most importantly for the present investigation, we have found that choice procedures in rats are well suited to comparing acute vs. chronic effects of pharmacological manipulations: we previously used a choice procedure to compare acute and subchronic effects of d-amphetamine, and of the D_2/D_3 partial agonist aripiprazole, obtaining results in line with human studies (Thomsen et al., 2008; 2013; Greenwald et al., 2010; Haney et al., 2011). Other evidence also supports a concordance between effects of medication maintenance on cocaine choice in preclinical studies, cocaine choice in human laboratory studies, and cocaine use in clinical trials (Foltin et al., 2015; Johnson et al., 2016; Czoty et al., 2016; Lile et al., 2016).

The primary objective of the present study was to evaluate dopamine D_3 receptor-selective (or D_3-preferring) ligands, both agonist and antagonist, as a continuous (sub)chronic treatment, in a direct comparison with D_2 receptor ligands. The effects of chronic administration were also compared to acute dosing effects. **Table 1** shows the ligands tested and their respective affinities for D_2 and D_3 receptors, from previously published sources. All compounds penetrate the blood-brain barrier, except for RGH-237 that showed poor brain penetration, but still showed behavioral effects consistent with partial D_3 receptor agonist activity (Heidbreder and Newman, 2010; Mason et al., 2010; Morgan and Van Der Graaf, 2012; and see Table 1 references). The hypothesis being tested was that D_2 and D_3 receptor ligands would differ

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in chronic as well as acute effects, and, specifically, that chronic administration of a D_3 receptor ligand could decrease cocaine self-administration in the cocaine vs. food choice procedure in rats.

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METHODS AND MATERIALS

Animals. Experimentally naïve male Sprague-Dawley rats were acquired at 8 weeks of age from Charles River laboratories (Wilmington, MA) and acclimated to the laboratory for at least a week before training began. Rats were housed individually with free access to water in a temperature- and humidity-controlled facility maintained on a 12-h light/dark cycle (lights on at 07:00). Rats were fed ≈17g standard rat chow daily (Rat Diet 5001; PMI Feeds, Inc., St. Louis, MO), adjusted to maintain a healthy 400-500g bodyweight. For enrichment, "treats" were provided once or twice weekly, typically Bacon-flavored biscuits (5g, Bio-Serve, Frenchtown, NJ). Behavioral testing was conducted during the light phase. Husbandry and testing complied with the guidelines of the National Institutes of Health Committee on Laboratory Animal Resources, and all protocols were approved by the McLean Hospital Institutional Animal Care and Use Committee.

Apparatus. Operant conditioning chambers (21 cm x 29.5 cm x 24.5 cm) and associated hardware from MED Associates (Georgia, VT) were placed within sound-attenuating cubicles equipped with a house light and an exhaust fan. Each chamber contained three response levers 3 cm above the grid floor, two "reinforcer" levers (referred to as the "left" and "right" levers) on one wall and a third "observer" lever centered on the opposite wall. A steel cup between the reinforcer levers, 2 cm above the floor, served as a receptacle for the delivery and consumption of liquid food reinforcers. A three-light array (red, yellow, and green) was located above the right lever and illuminated to signify the availability food. An identical array with one additional yellow light was located above the left lever and was used to signal the cocaine dose available. A white light was located above the observer lever. Each cubicle also contained two syringe pumps (3.3 rpm, model PHM-100), for the delivery of liquid food and intravenous cocaine, respectively, through Tygon tubing. Cocaine was delivered using a single-channel fluid swivel (MS-1, Lomir Biomedical, Malone, NY) mounted on a balance arm, which allowed rats free movement.

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Operant training and surgery. Rats were trained and tested in a cocaine vs. choice food procedure as previously described (Thomsen et al., 2008; 2013; 2014). Between completion of the acute dosing experiments and beginning the chronic dosing experiments, the procedure was slightly modified, in two ways to allow for more efficient training: 1) acute experiments used static levers, while retractable levers were used in the chronic experiments; 2) the reinforcer magnitudes (food concentration and cocaine doses) were adjusted slightly (see below). All other parameters and training methods were identical, and as briefly outlined below:

Food training. First, lever pressing was acquired in daily 2-h sessions, with liquid food (75 µl of vanilla flavor Ensure® nutrition drink, Abbott Laboratories, Abbott, IL) reinforcing responding under an FR 1 schedule of reinforcement. Food was diluted to 56% in water for acute dosing experiments and to 32% for chronic experiments. Illumination of the triple cue light above the right lever signaled food availability, cues were turned off at reinforcer delivery. Responses on the other levers (cues off) were recorded but had no scheduled consequences. When ≥50 reinforcers were earned within one 2-h session, the response requirement was gradually increased to FR 5. When rats again earned ≥50 reinforcers, a chain schedule was introduced in which one response on the observer lever initiated an FR 5 schedule on the right lever (see Thomsen et al., 2013 for details). When rats again earned ≥50 food reinforcers per session for five consecutive sessions (training criteria), they were implanted with catheters.

Surgery and catheter maintenance. Rats were anesthetized with an isoflurane/oxygen vapor mixture and implanted with chronic indwelling jugular vein catheters (see Thomsen and Caine, 2005). A catheter was inserted 3.7 cm into the external jugular vein and anchored to the vein. The catheter ran subcutaneously to the midscapular region where the base was located. Single doses of analgesic (ketoprofen 5 mg/kg) and antibiotic (amikacin 10 mg/kg) were administered subcutaneously immediately before surgery. Rats were allowed ≈7 days of recovery before being given access to intravenous cocaine. During this period, a prophylactic dose of cefazolin (30-40 mg/kg) was delivered daily through the catheter. Thereafter, catheters were flushed daily with sterile saline containing heparin (3 USP U/0.1 ml). Catheter patency was verified daily by withdrawing and immediately re-infusing a few microliters of

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blood through the catheter (enough for visual detection of blood); if blood could not be withdrawn, catheter patency was tested by administering 0.05-0.1 ml of a ketamine-midazolam mixture (15 + 0.75 mg/ml) through the catheter and observing prominent signs of sedation within 3 seconds of infusion. Only data collected with demonstrated patent catheters were included.

Cocaine Self-Administration Training. Cocaine self-administration started with daily 2-h sessions, under an FR 1 FR 1 timeout 20s chain schedule, left lever active. Responses on the right lever were recorded and reset the ratio requirement on the left lever. Sessions started with a noncontingent "priming" cocaine infusion, then, flashing of the full cue light array over the left lever indicated availability of 1.0 mg/kg/infusion cocaine. Cues were turned off at reinforcer delivery. The response requirement was gradually increased to FR 1 FR 5, and training continued until cocaine self-administration behavior stabilized, defined as three consecutive sessions with ≥10 mg/kg cocaine self-administered per 2-h session and ≥90% of left+right lever responses emitted on the drug-reinforced lever. Sessions were then modified to include five 20-min components of cocaine availability (1.0 mg/kg/infusion), with 2-min inter-component timeout periods, using the same schedule of reinforcement. This schedule remained in effect until behavior stabilized, i.e., ≥10 mg/kg cocaine self-administered per session and ≥1 reinforcer earned per component. Rats were then given access to 0.32 mg/kg/infusion cocaine for at least one day before choice training began, to observe increased rates of responding.

*Cocaine vs. Food Choice Training***.** Daily sessions consisted of five 20-min components separated by 2-min timeout periods. Responding was reinforced under FR 1 concurrent FR 5 FR 5 chain schedule, responding on the right lever being reinforced with liquid food, responding on the left being reinforced with cocaine infusions of increasing dose for each component: 0, 0.032, 0.1, 0.32, 1.0 mg/kg/infusion (acute experiment), or 0, 0.056, 0.18, 0.56, 1.0 mg/kg/infusion (chronic experiment). Responding on one reinforcer lever reset the ratio requirement on the other. Cocaine doses were achieved by varying the infusion time, adjusted to each rat's bodyweight. The light array over the left lever flashed when cocaine was available, indicating the unit dose available: no light for 0, green for 0.032/0.056, green+yellow for 0.10/0.18, green+yellow+red for 0.32/0.56, and green+yellow+red+yellow for 1.0 mg/kg/infusion; cues

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were turned off at reinforcer delivery. Per component, 15 total reinforcers were available (completion of the response requirement on the left lever during availability of the zero cocaine dose counted as one reinforcer). If all 15 reinforcers were earned in less than 20 min, all stimulus lights were extinguished, and responding had no scheduled consequences for the remainder of the 20-min component. Choice training continued until behavior stabilized satisfying: three consecutive sessions with ≥5 reinforcers/component earned in components 1-4 and ≥1 reinforcer earned in component 5, and with the dose of cocaine producing ≥80% cocaine choice on any given day remaining within one-half log unit of the 3-day mean.

Testing. Once training was completed, we tested the effects of D_2- and D_3-preferring agonists, partial agonists, and antagonists, under acute and chronic dosing conditions. Rats were allocated to test groups randomly. As much as possible, doses of each drug were tested within-subjects, but due to attrition, additional rats had to be added to some dose groups. Rat had at least three sessions of baseline between acute doses or at least one week between chronic doses. Baseline choice behavior had to satisfy the original criteria (see above) in order for a rat to test again. If the cocaine dose maintaining ≥80% cocaine choice was within one-half log unit of the previously established baseline, a rat could test again; if not, a new stable 3-day baseline was established with the criteria described above.

In the acute treatment experiment, we tested the D_2 agonist R(-)-norpropylapomorphine (NPA; 0.01, 0.032, 0.1, 0.32, 0.56 and 1.0 mg/kg), the D_2/D_3 partial agonist terguride (0.032, 0.1, 0.32, 0.56, 1.0 mg/kg), the D_2 antagonist L-741,626 (0.32, 1.0, 3.2, 5.6 mg/kg), the D_3 agonist PD-128,907 (0.1, 0.32, 1.0, 3.2, 5.6 mg/kg), the D_3 partial agonist RGH-237 (10, 32, 56 mg/kg), and the D_3 antagonist PG01037 (1.0, 3.2, 10, 18, 32 mg/kg), as well as corresponding vehicles, with doses presented in counterbalanced sequence. All drugs were administered intraperitoneally, 10 min before the session.

In the chronic treatment experiment, the D_3-preferring agonist PD-128,907 was replaced by the then newly available, more selective D_3 agonist PF-592,379 (Attkins et al., 2010). We have previously reported the effects of acute and chronic administration of the partial D_2/D_3 agonist aripiprazole using the same assay (Thomsen et al. 2008), therefore partial agonists were not evaluated as chronic treatment in

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the present investigation. Chronic treatment was achieved with the use of osmotic minipumps (Alzet model 2ML1; Durect, Cupertino, CA) that were implanted subcutaneously under brief isoflurane/oxygen vapor anesthesia, and delivered drug continuously at a rate of 10 µl/h. Before implantation, filled minipumps were primed overnight in sterile 0.9% saline at 37-38ºC as directed by the manufacturer. On day 1, rats were tested 2 h after pump implantation, then, pumps were left in place for 7 days, during which time rats were tested daily as they had been during training. Chronic treatments tested were as follows: NPA (0.00032, 0.001, 0.0032, 0.01 mg/kg/h), L-741,626 (0.056, 0.18, 0.32, 0.56 mg/kg/h), PF-592,379 (0.56, 1.8, 3.2 mg/kg/h), and PG01037 (0.56, 1.8, 3.2, 5.6 mg/kg/h). Drug concentrations were adjusted for each rat according to bodyweight. Treatment was stopped by removing the minipump. We previously verified that 7 days of continuous water administration and presence of the minipumps did not produce any significant changes in choice behavior (Thomsen et al., 2013), and the present data set includes low doses that showed no effect (e.g., NPA, PF-592,379). Therefore, to reduce the number of animal lives needed, we did not include further chronic vehicle groups. Data are reported for the first and last day for brevity, and intervening days typically showed gradual shifts from the acute effects to the chronic effects.

Drugs. Cocaine hydrochloride was provided by NIDA/NIH (Bethesda, MD). PF-592,379 was supplied by P. Butler and was synthesized as previously described at Pfizer, Sandwich, UK (Attkins et al., 2010). PG01037 dihydrochloride was supplied by A.H. Newman and was synthesized as previously described at the Medicinal Chemistry Section, National Institute on Drug Abuse, National Institutes of Health (NIDA/NIH), Baltimore, Maryland, USA (Grundt et al., 2005). RGH-237 was supplied by I. Gyertyán and synthesized as previously described at Gedeon Richter, Budapest, Hungary (Gyertyán et al., 2007). All other drugs were purchased from Sigma-Aldrich (St Louis, MO). Cocaine and terguride were dissolved in 0.9% saline. PF-592,379, PD-128,907 hydrochloride, and PG01037 dihydrochloride were dissolved in sterile water. NPA hydrochloride was dissolved in 0.1% ascorbic acid in water, L-741,626 was dissolved in 22% β-cyclodextrin in water, and RGH-237 was dissolved in ethanol and diluted to a

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final vehicle of 5% ethanol, 47.5% polyethylene glycol and 47.5% water. Doses reflect the weights of the respective salts.

Data Analysis. The primary dependent variables recorded for each component were: (1) number of cocaine injections earned, (2) number of food reinforcers earned, and (3) percent cocaine choice, calculated as (number of ratios completed on the cocaine-associated lever ÷ total number of ratios completed) x 100. Total cocaine intake per session (mg/kg) and total food reinforcers earned per session, were also calculated for each rat. Total response rate (total number of responses ÷ total time responses had scheduled consequences) and response rate on the reinforcer levers alone (calculated using the time these levers were extended) were also recorded, but are not reported because they added no significant information on treatment effects, relative to numbers of reinforcers earned. Significance level was set at $P<0.05$. No data points collected with patent catheters were excluded (no "outliers").

For the acute treatments, two-way ANOVA was used to analyze the effects of test drugs and cocaine dose on numbers of cocaine and food reinforcers earned per component, factors being cocaine dose (repeated measures, within-subjects) and treatment dose (between-subjects). For the chronic experiment, repeated measures two-way ANOVA was used to analyze the effects of test drugs and cocaine dose on numbers of cocaine and food reinforcers earned per component, factors being cocaine dose and treatment day (i.e., baseline, first day, after one week). Because all doses of a test compound could not always be tested in each rat (within-subject), each chronic drug dose was analyzed separately, so that test vs. baseline could be analyzed within-subjects. Significant effects on a test day were scrutinized post-hoc by Bonferroni posttest vs. vehicle/baseline. In both acute and chronic experiments, the effect of cocaine dose was always highly significant and is not reported for each analysis, for brevity.

The percent cocaine choice data was used to calculate A_{50} values (potency), defined as the dose of cocaine that produced 50% cocaine choice in each rat, and determined by interpolation from two adjacent points spanning 50% cocaine choice. In cases where cocaine choice was 50-60% at the lowest dose, extrapolation was used (<4% of all values). In cases where cocaine choice was >60% at the lowest dose, a

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value of 0.018 or 0.032 mg/kg/injection was assigned (i.e., quarter-log below the lowest cocaine dose tested, in the acute and chronic experiments, respectively) as a conservative estimate; because many treatments, especially chronic, produced leftward shifts in the cocaine choice curve, these estimates amounted to 16% of all A_{50} values. Similarly in cases where cocaine choice was <40% at the highest dose, a value of 1.8 mg/kg/injection was assigned (2 values, <0.5% of total). Group means and 95% confidence intervals were calculated from the log(10) of individual A_{50} values, but are reported transformed back to linear values for ease of reading. In some cases, responding was completely suppressed in one or more rats for some time/dose points, resulting in missing values for the choice measure, precluding the use of repeated measures ANOVA for this measure. Instead, the log-transformed A_{50} values were compared by one-way ANOVA for the acute experiment (factor: dose, between-subjects), and two-way ANOVA for the chronic experiment (factors: treatment dose, between-subjects; test day, within-subjects, using pooled baseline data for all rats tested with any dose of that drug). Significant effects or interactions were examined by one-way ANOVA for each time point. Significant effects were followed by Dunnett's multiple comparisons test vs. vehicle or baseline. Total cocaine intake and total food reinforcers earned per session were analyzed in the same way as A_{50} values.

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RESULTS

Acute administration

In a first experiment, we tested the acute effects of pretreatment with D_2 and D_3 agonists, partial agonists, and antagonists on cocaine vs. food choice. **Figure 1** shows the effects of the D_2 agonist NPA, the D_2/D_3 partial agonist terguride, and the D_2 antagonist L-741,626 on numbers of cocaine injections and food reinforcers earned, and percent cocaine choice. To avoid crowding, three doses were selected for graphical presentation for each ligand, omitting some low and/or intermediate doses. Likewise, **Figure 2** shows the effects the D_3 agonist PD-128,907, the D_3 partial agonist RGH-237, and the D_3 antagonist PG01037. The corresponding potencies of cocaine to produce 50% cocaine choice (A_{50} values) are reported in **Table 2** (all doses tested). Total cocaine intake per session and total food reinforcers were also calculated, and are presented in **Figure 3** for all doses tested.

The D_2 agonist NPA produced dose-dependent leftward shifts in the cocaine reinforcers dose-effect curve, with a significant cocaine dose by NPA dose interaction (intx) [$F(24,140)=2.29$, $P<0.01$]; effects of 0.32, 056 and 1.0 mg/kg reached significance post hoc ($P<0.01$; **Figure 1**). NPA also produced marked decreases in numbers of food reinforcers earned (NPA dose [$F(6,140)=9.47$, $P<0.0001$], intx [$F(24,140)=3.71$, $P<0.0001$]), with doses from 0.032 mg/kg and up producing significant decreases ($P<0.01$). This reallocation of behavior from food towards cocaine resulted in dose-dependent leftward shifts in the cocaine choice curve, with corresponding decreases in A_{50} values [$F(6,32)=3.92$, $P<0.01$], see **Table 2** for statistical analysis. NPA's effects on reinforcers earned resulted in dose-dependent decreases in both total cocaine intake [$F(6,35)=2.94$, $P<0.05$] and total food reinforcers earned [$F(6,35)=9.49$, $P<0.0001$], although post-hoc comparisons on cocaine intake did not reach significance (**Figure 3**).

The D_2/D_3 partial agonist terguride did not affect cocaine reinforcers earned significantly, up to doses that significantly suppressed food reinforcers (terguride dose [$F(5,128)=9.30$, $P<0.0001$], intx [$F(20,128)=5.74$, $P<0.0001$]), significant at 0.1, 0.56 and 1.0 mg/kg ($P<0.05$). Terguride did not affect cocaine choice curves or A_{50} values consistently or significantly (**Table 2**). Terguride also failed to affect

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total cocaine intake significantly, but did produce significant decreases in total food reinforcers earned [F(5,31)=10.7, P<0.0001] (see **Figure 3**).

The D_2 antagonist L-741,626 produced effects opposite to NPA on the cocaine reinforcers curve, i.e., dose-dependent rightward shifts (L-741,626 dose [F(4,136)=4.74, P<0.01], intx [F(16,136)=5.98, P<0.0001]. Effects of 3.2 and 5.6 mg/kg reached significance (P<0.001; **Figure 1**). L-741,626 also decreased the numbers of food reinforcers earned (L-741-626 dose [F(4,136)=12.0, P<0.0001], intx [F(16,136)=5.64, P<0.0001]), at the same dose that affected cocaine reinforcers, 3.2 and 5.6 mg/kg (P<0.05 and less). The combined effect on the cocaine choice curve was dose-dependent rightward shifts with corresponding increases in A_{50} values [F(3,27)=2.91, P=0.05], significant at the highest dose (P<0.05; **Table 2**). Although intermediate doses of L-741,626 increased the number of high-dose cocaine injections earned, total cocaine intake was only increased marginally; however, the highest dose of L-741,626 decreased cocaine intake [F(4,40)=5.12, P<0.01]. The same profile was apparent for total food reinforcers earned [F(4,40)=18.0, P<0.0001], see **Figure 3**.

The D_3 agonist PD-128,907 produced downward shifts in the cocaine reinforcer curve at intermediate doses, and a downward/leftward shift at the highest dose (treatment by cocaine intx [F(20,160)=2.32, P<0.001]). Effects were significant at 0.32, 3.2, and 5.6 mg/kg (P<0.05, **Figure 2**). PD-128,907 also produced marked downward and downward/rightward shifts in the food reinforcers curve (PD-128,907 dose [F(5,160)=6.69, p=0.0001], intx [F(20,160)=4.79, P<0.0001], with significant effects at doses from 0.1 mg/kg and up (P<0.05). The effect on percent cocaine choice was mixed, with small, non-significant rightward shifts at intermediate doses, and significant leftward shifts at the higher doses. Thus, PD-128,907 modulated A_{50} values [F(5,35)=3.62, P<0.01], with a significant decrease at 5.6 mg/kg (See **Table 2**). Effects of PD-128,907 on total cocaine intake were modest and not statistically significant (**Figure 3**), while effects on food were more pronounced [F(5,41)=7.02, P<0001].

The D_3 partial agonist RGH-237 and the D_3 antagonist PG01037 each produced moderate, non-significant leftward shifts in the cocaine reinforcer curve at lower doses, and moderate downward shifts at high doses (**Figure 2**). However, the effect reached significance only for RGH-237 (intx [F(12,112)=1.90,

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P<0.05]), the highest dose of 56 mg/kg producing a significant downward shift (*P*<0.05). Both ligands dose-dependently decreased the number of food reinforcers earned (RGH-237 by cocaine intx [F(12,112)=1.92, *P*<0.05]; PG01037 dose [F(5,136)=17.0, *p*=0.0001], intx [F(20,136)=5.43, *P*<0.0001]). RGH-237 produced significant decreases at 10 and 56 mg/kg (*P*<0.05), PG01037, at 18 and 32 mg/kg (*P*<0.0001). Neither ligand affected cocaine choice curves or A_{50} values systematically or significantly (**Table 2**). Likewise, neither drug affected total cocaine intake significantly, but PG01037 did decrease total food reinforcers earned dose-dependently [F(5,35)=17.9, *P*<0.0001], as shown in **Figure 3**.

Chronic administration

Figure 4 shows the acute and chronic effects of continuous administration of the D_2 agonist NPA and the D_2 antagonist L-741,626 on numbers of cocaine injections and food reinforcers earned, and percent cocaine choice, as a function of treatment dose (one dose per panel "column"). **Figure 5** shows the acute and chronic effects of continuous administration of the D_3 agonist PF-592,379 and the D_3 antagonist PG01037 in the same fashion. Data are reported for the first and last day for brevity, and intervening days typically showed gradual shifts from the acute effects to the chronic effects.

The corresponding potencies of cocaine to produce 50% cocaine choice (A_{50} values) are reported in **Table 3**. Total-session cocaine intake and total food reinforcers were also calculated, and are presented in **Figure 6**.

The D_2 agonist NPA produced leftward and downward shifts in the cocaine self-administration curve, with marked tolerance after a week of treatment. Cocaine reinforcers were affected significantly at the two highest doses, as a function of treatment day: at 0.0032 mg/kg/h (cocaine dose by treatment intx [F(8,50)=4.05, *P*<0.001]) and at 0.01 mg/kg/h (treatment [F(2,50)=13.4, *P*<0.0001], intx [F(8,50)=3.87, *P*<0.01]). In the same dose range, NPA significantly decreased the number of food reinforcers earned, but this effect was not generally diminished after chronic administration: at 0.0032 mg/kg/h (treatment [F(2,50)=8.10, *P*<0.001], intx [F(8,50)=3.87, *P*<0.01]), and at 0.01 mg/kg/h ([main F(2,50)=4.32, *P*<0.05, intx F(8,50)=2.92, *P*<0.001]). Percent cocaine choice was shifted to the left, with corresponding

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decreases in A_{50} values (treatment day [F(1,30)=5.20, $P<0.05$]), although the effect did not reach statistical significance on specific days (**Table 3)**. The shift in the cocaine dose-effect curve towards the lower cocaine doses resulted in a significant decrease in total cocaine intake on day 1, but this effect was abolished after a week of treatment (see **Figure 6**; effect of treatment dose, treatment time, and intx all $p\leq0.001$). Total food intake was decreased as a function of NPA dose [F4,60)=3.04, $P<0.05$], with no effect of treatment time or dose by time interaction (i.e., no significant tolerance).

Conversely, the D_2 antagonist L-741,626 produced rightward shifts in the cocaine curve, which showed a high degree of tolerance up until the highest dose, 0.56 mg/kg/h, which produced a downward shift only as chronic treatment, suggesting drug accumulation or perhaps sensitization (see **Figure 4** for statistical details). L-741,626 also decreased the number of food reinforcers earned, and this effect showed tolerance only at the two lowest doses. In fact, exacerbation of the effect upon chronic administration was apparent at the higher doses. L-741,626 also affected cocaine choice, as measured by A_{50} values, differentially as acute and chronic treatment (2-way ANOVA, effect of L-741,626 dose [F(3,28)=4.42, $P<0.05$], treatment day [F(1,28)=12.1, $P<0.01$], and dose by time intx [F(3,28)=3.46, $P<0.05$]). Specifically, choice curves were shifted to the right, and A_{50} values increased, on day 1 [F(4,31)=4.09, $P<0.01$], with the converse effect after one week of treatment [F(3,28)=3.12, $P<0.05$] (see **Table 3**). As shown in **Figure 6**, the rightward shift in the cocaine curve (i.e., shift towards higher cocaine doses) resulted in an increase in total cocaine intake acutely, and this effect dissipated after chronic administration (L-741,626 dose by time intx [F(4,31)=3.55, $P<0.05$]). Total food intake was decreased both acutely and chronically (see **Figure 6**; effect of treatment dose [F(4,31)=8.41, $p=0.0001$], dose by time intx [F(4,31)=3.68, $P<0.05$]).

The D_3 agonist PF-592,379 had no effect on numbers of cocaine injections earned acutely, up to doses that decreased food reinforcers. However, the highest dose, 3.2 mg/kg/h, produced a leftward or upward shift in the ascending limb of the cocaine dose-effect curve after a week of continuous administration (see **Figure 5**; treatment [F(2,40)=5.89, $P<0.01$], intx [F(8,40)=5.91, $P<0.0001$]). This

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shift was not accompanied by a decrease in the high-dose cocaine injections (descending limb). A trend towards the same effect was apparent at the intermediate dose of 1.8 mg/kg/h. Food reinforcers similarly were only affected significantly at the highest dose, which produced a decrease both acutely and chronically (treatment [F(2,40)=8.79, $P<0.001$], intx [F(8,40)=3.79, $P<0.01$]). Thus, after chronic treatment with the D_3 agonist, behavior was reallocated from food towards cocaine taking, and percent cocaine choice was shifted leftwards, with decreased A_{50} values (2-way ANOVA effect of treatment day [F(1,21)=5.78, $P<0.05$] and dose [F(3,21)=1.22, $P<0.05$]), significant after chronic administration only [F(13,21)=5.94, $P<0.01$], **Table 3**). Despite this shift, seen only at the lowest unit dose cocaine, total cocaine intake was not significantly modified by PF-592,379, acutely or chronically (**Figure 6**). Food intake was suppressed moderately, and as much or more so by chronic administration relative to acute (effect of PF-592,379 dose [F(3,21)=4.43, $P<0.05$]).

The D_3 antagonist PG01037 had no effect on numbers of cocaine injections earned at most doses, acutely or chronically, but did produce a downward shift in the cocaine curve at the intermediate-high dose of 3.2 mg/kg/h, with partial tolerance after one week of treatment (treatment day [F(2,50)=4.86, $P<0.05$], intx [F(8,50)=2.45, $P<0.05$]). This decrease in cocaine choice was accompanied by a moderate and non-significant increase in food reinforcers. However, the highest dose, 5.6 mg/kg/h PG01037, decreased food-reinforced behavior significantly without affecting cocaine, and this effect on food remained as pronounced or more pronounced after one week (see **Figure 5**; treatment [F(2,30)=17.4, $p=0.0001$], intx [F(8,30)=5.99, $P<0.0001$]). Consequently, percent cocaine choice was shifted moderately to the right at the 3.2 mg/kg/h treatment, as supported by a significant increase in A_{50} values (effect of dose PG01037 [F(4,37)=2.85, $P<0.05$, see **Table 3**]). The 0.56 and 1.8 mg/kg/h doses produced only modest, non-significant rightward shifts in the cocaine choice curve, indicating a narrow dose window or variable effect of PG01037. While 3.2 mg/kg/h appeared to be the most effective dose across rats, some individual variability was observed, with some rats indicating a decrease in cocaine self-administration at lower doses. The shift produced by 3.2 mg/kg/h was much attenuated after chronic treatment, and only statistically significant on day 1 [F(4,37)=4.58, $P<0.01$], see **Table 3**. Regardless of treatment time,

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PG01037 treatment failed to significantly alter total cocaine intake per session, while food intake was decreased at the highest dose of PG01037 (effect of dose [$F(4,38)=3.62$, $P<0.05$] (**Figure 6**).

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DISCUSSION

The dopamine D_3 receptor continues to be of interest as a potential target for cocaine addiction medications. D_3 receptor antagonists have generally failed to decrease the direct reinforcing effects of cocaine, but can decrease conditioned responding (for review, see Sokoloff and Le Foll, 2016). However, the evaluation of D_3 receptor ligands has mostly concentrated on acute dosing. Preclinical and clinical studies have demonstrated that chronic administration of dopamine receptor ligands, and dopamine transporter ligands, can affect cocaine intake and other addiction-related effects of cocaine very differently from their acute effects. Non-selective dopamine receptor antagonists (e.g., flupenthixol), D_2 receptor antagonists (e.g., risperidone), and D_1/D_5 receptor antagonists (SCH 39166, SCH 23390), have been evaluated preclinically and clinically. All showed antagonism of cocaine's effects, including reduced self-administration, as acute dosing, but were ineffective or increased cocaine intake and/or subjective effects of cocaine as chronic treatment, with good agreement between human studies (Romach et al., 1999; Grabowski et al., 2000; Haney et al., 2001; Nann-Vernotica et al., 2001; Loebl et al., 2008; Kishi et al., 2013) and laboratory animal studies (Kleven and Woolverton, 1990; Negus et al., 1996; Negus, 2003; Hutsell et al., 2016). Similar effects were obtained with the D_2/D_3 partial agonist aripiprazole (Stoops et al., 2007; Bergman et al., 2008; Thomsen et al., 2008; Haney et al., 2011; Lofwall et al., 2014).

Conversely to dopamine receptor antagonists, agonist medication strategies using chronic administration of monoamine releasers such as D-amphetamine, methamphetamine, phenmetrazine, or their pro-drugs, decreased cocaine taking and cocaine choice in humans (Grabowski et al., 2001; Shearer et al., 2003; Mooney et al., 2009; Greenwald et al., 2010; Pérez-Maña et al., 2011; Nuijten et al., 2016), monkeys (Negus, 2003; Negus and Mello, 2003; Czoty et al., 2010, 2011; Banks et al., 2011, 2013, 2015b; Hutsell et al., 2016), and rats (Chiodo et al., 2008; Thomsen et al., 2013). Acutely, amphetamines mimic and increase behavioral and subjective effects of cocaine and increase cocaine intake/choice (Barrett et al., 2004; Thomsen et al., 2013). Thus, both agonist and antagonist dopaminergic manipulations show either profound tolerance, or indeed a complete reversal of effect direction between acute and chronic administration. Therefore, it is becoming clear that potential cocaine addiction

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medication strategies must be evaluated using chronic or subchronic dosing conditions to better predict effects of clinical use, in which medications will most likely be administered as chronic treatment to promote abstinence.

While there is mounting evidence to support the efficacy of agonist medications with psychostimulant properties such as d-amphetamine (but not of direct dopamine receptor agonists), the acceptance and FDA approval of those drugs are faced with serious challenges based on concerns about their addictive potential and safety (Pérez-Maña et al., 2011; Minozzi et al., 2015; Negus and Henningfield, 2015). Here, we compared acute and chronic dosing effects of dopamine D_2 and D_3 receptor agonists and antagonists, using a cocaine vs. food choice assay in rats. A primary objective of these studies was to evaluate D_3 receptor agonists and antagonists as (sub)chronic treatments, and test the hypothesis that chronic administration may decrease cocaine choice and/or intake, despite the general lack of acute effect of D_3 receptor-selective ligands on cocaine self-administration. D_2 receptor agonists and antagonists were also tested using acute and chronic treatment regimens to allow for direct comparisons.

A summary of treatment effects in the present investigation is presented in Table 4, as well as previous results obtained with aripiprazole and *d*-amphetamine, for comparison. Acute dosing with D_2 receptor ligands produced results in agreement with previous single-reinforcer experiments (Caine et al., 2000; Haile and Kosten, 2001; Barrett et al., 2004; Rowlett et al., 2007): the agonist NPA shifted the cocaine self-administration dose-effect curve to the left, the antagonist L-741,626 shifted the curve to the right, and the partial agonist had little effect. All three compounds also suppressed food-reinforced responding, also consistent with single-reinforcer studies (Barrett et al., 2004). Acute effects of the D_3 receptor ligands differed from this typical agonist/antagonist profile. A flattening of the cocaine self-administration curve was observed with the highest dose of the agonist PD-128,907 and with lower doses of both the partial agonist RGH-237 and of the antagonist PG01037. The variable and non-significant increase in self-administration of a low dose of cocaine most likely reflects modulation of the conditioned reinforcing effects of the cocaine-associated cues, rather than an increase in the reinforcing effect of cocaine or direct reinforcing effects of the D_3 receptor ligand, based on previous studies failing to

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demonstrate reinforcing effects of D_3 receptor-selective ligands, as well as the fact that cocaine choices were not increased in the no-cocaine component in the present investigation (Beardsley et al., 2001; Collins and Woods, 2009; Collins et al., 2012). Lower doses of PD-128,907 and higher doses of RGH-237 or PG01037 produced downward shifts of similar magnitude in cocaine and food choices, suggesting non-selective suppression of behavior rather than modulation of cocaine's reinforcing effects specifically. This is consistent with a general lack of effect of D_3 receptor ligands in single-reinforcer cocaine self-administration studies in monkeys and rodents at doses that did not also cause general suppression of behavior (Beardsley et al., 2001; Gál and Gyertyán, 2003; Achat-Mendes et al., 2009; Caine et al., 2012). It is also possible that both stimulation and blockade of D_3 receptors can mediate a moderating effect on reward pathways, at least in rats. Although speculative, this notion of D_3 systems as performing a "dampening", modulatory function is consistent with both PD-128,907 and PG01037 decreasing ICSS acutely in rats (Lazenka et al., 2016).

Chronic administration of a D_2 receptor agonist (NPA) or antagonist (L741,626) also produced effects in agreement with previous studies in monkeys. For example, in agreement with the present study, chronic 5-day treatment with NPA in rhesus monkeys initially shifted the cocaine self-administration curve to the left and down and decreased cocaine intake, but tolerance developed after 5-day administration, at least in subordinate monkeys (Czoty and Nader, 2013). NPA also produced some cocaine-lever choice during the first component, both acutely and after continuous administration, when no cocaine was available. This is consistent with acute effects of D_2-family receptor agonists in rats and monkeys under similar conditions, and with NPA functioning as a positive reinforcer in monkeys (Weissenborn et al., 1996; Gasior et al., 2004; Barrett et al., 2004; Rowlett et al., 2007). Consistent with the present findings using L741,626, chronic L741,626 or eticlopride suppressed food- and cocaine-reinforced responding nonselectively in monkeys (Claytor et al., 2006; Achat-Mendes et al., 2010). Despite an initial decrease in cocaine choice with one dose L741,626 in the present study, both NPA and L741,626, if anything, increased % cocaine choice after continuous administration, and neither decreased total cocaine intake.

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Chronic administration of a D_3 receptor agonist (PF-592,379) or antagonist (PG01037) also produced effects distinct from the D_2 ligands. Acutely, PF-592,379 moderately decreased food choices with no effect on cocaine, but chronic PF-592,379 increased self-administration of low doses of cocaine while further decreasing food choices. This undesirable profile is in agreement with the effects of a D_3-preferring partial agonist in monkeys, and of 15-day treatment with pramipexole, which strongly increased positive subjective effects of cocaine in humans (Achat-Mendes et al., 2009; Newton et al., 2015). Unlike NPA, PF-592,379 produced little responding on the cocaine-associated lever during the first component, consistent with the notion that D_3-preferring agonists can enhance the conditioned reinforcing effects of cocaine-associated cues, but maintain little responding *per se* (Collins and Woods, 2009; Collins et al., 2012). Consistent with the acute dosing data and with previous single-reinforcer studies in monkeys, PG01037 had minimal effects on cocaine self-administration up to doses that also suppressed food-reinforced responding (Achat-Mendes et al., 2010). However, consistent with choice studies in monkeys, 3.2 mg/kg PG01037 produced a significant downward shift in the cocaine curve, with tolerance after continuous administration (Czoty and Nader, 2015; John et al., 2015a). A higher dose suppressed responding nonselectively. Although effects on food did not reach statistical significance, it is perhaps worth noting that PG01037 was the only treatment that increased food intake after chronic administration in the present studies, while L741,626 mostly decreased food-reinforced responding. This is consistent with recent studies using dopamine receptor knockout mice, which indicated that D_2, rather D_3 or D_4 receptors, mediate reinforcing effects of food (Soto et al., 2015).

In terms of total cocaine intake and overall food-reinforced behavior, none of the treatment regimens offered promising medication-like profiles in this assay. Up to doses that disrupted food-reinforced behavior, no compound decreased cocaine intake significantly. Similarly, the 5-HT_{1A} agonist and D_3/D_4 antagonist buspirone reduced cocaine self-administration in monkeys acutely, but increased cocaine choice after 5-day treatment, and failed to improve time to relapse or cocaine-taking in clinical trials (Bergman et al., 2013; Winhusen et al., 2014; John et al., 2015b; Bolin et al., 2016; but see Mello et al., 2013). In fact, buspirone increased cocaine use in women (Winhusen et al., 2014). One possible

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reason for the variable and typically modest effects of PG01037 and other D_3 receptor antagonists may be highly variable sensitivity between individuals, which was observed here and in monkeys (Czoty and Nader, 2015; John et al., 2015a). For all compounds tested, the effects of high doses on food-reinforced behavior persisted or increased during chronic administration. Although blood drug levels were not measured, it is likely that some or all ligands were tested up to doses that produced moderate drug accumulation, although the development of sensitization rather than tolerance is also possible. Drug accumulation is most likely to have occurred for L-741,626 and PF-592,379 based on pilot pharmacokinetic studies (PF-592,379) and the observation that rats typically required at least three days to re-establish baseline levels of responding after minipump removal with those ligands. Regardless of mechanism, the dissociation of chronic effects on cocaine and food indicates that distinct pharmacological mechanisms underlie effects on cocaine and non-drug reinforcement. Unfortunately, this profile may suggest that dose-limiting, undesirable effects of dopamine receptor ligands in humans may also be resistant to tolerance.

In conclusion, the cocaine vs. food choice procedure in rats produced data consistent with studies in monkeys and human subjects. Further, these findings underline the importance of testing chronic or subchronic administration of compounds of interest, at the preclinical stage. In particular, both the D_2 antagonist L-741,626 and the D_3 antagonist PG01037 decreased cocaine choice at some dose as acute treatment, but after 1 week, neither drug significantly altered cocaine choice. Here, access to cocaine was not suspended during treatments, and it is possible that effects of chronic D_3 receptor antagonism could be larger if tested under suspended access conditions (Czoty and Nader, 2013). However, the difficulty in establishing abstinence in cocaine-dependent patients means that candidate medications should also be evaluated under conditions of continued cocaine access during treatment (Moran et al., 2016). Other factors that may influence the effectiveness of dopamine receptor ligands include feeding conditions, age, sex, and social status (Czoty and Nader, 2013, 2015; Baladi et al., 2014; Collins et al., 2014; Jupp et al., 2016), and the present data may not generalize to smaller/leaner subjects, females, etc. It would be of

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interest to examine cocaine self-administration behaviors of rats living in social groups, where access to social interactions, mating, etc. would arguably function as competing reinforcers.

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AUTHORSHIP CONTRIBUTIONS

Participated in research design: Caine, Negus, and Barrett.

Conducted experiments: Barrett, Caine.

Contributed new reagents or analytic tools: Butler.

Performed data analysis: Thomsen.

Wrote manuscript: Thomsen wrote the first draft, all authors contributed to and approved the final version.

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FOOTNOTES

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FIGURE LEGENDS

Figure 1

Acute dosing effects of dopamine D_2-preferring ligands on concurrent cocaine self-administration and food-reinforced responding as a function of cocaine dose. Abscissae: unit dose cocaine [mg/kg/injection]; ordinates: cocaine injections earned (top), food reinforcers earned (center), %cocaine choice (bottom), per component. Group sizes: see Table 2; choice data for higher pretreatment doses may be a lower group size due to missing values, and are not shown when responding was reduced to the point that %choice could be calculated for fewer than two mice. *P<0.05, **P<0.01, ***P<0.001 vs. vehicle, Bonferroni posttest following significant ANOVA.

Figure 2

Acute dosing effects of dopamine D_3-preferring ligands on concurrent cocaine self-administration (top panels) and food-reinforced responding (bottom panels) as a function of cocaine dose. Group sizes: see Table 2. Other details as in Figure 1.

Figure 3

Acute effects of dopamine D_2-preferring or D_3-preferring ligands on total cocaine intake and total food reinforcers per session. Abscissae: dose of pretreatment drug [mg/kg]; ordinates: total cocaine intake [mg/kg/session] (top) or total food reinforcers earned per session (bottom). Group sizes as in Table 2. *P<0.05, **P<0.01 Dunnett's multiple comparisons test vs. vehicle following significant ANOVA.

Figure 4

Acute vs. chronic effects of continuously administered dopamine D_2-preferring ligands on concurrent cocaine self-administration and food-reinforced responding. Data shown are baseline, day 1 (2 hours of administration), and day 7 (one week of continuous administration). Abscissae: unit dose cocaine

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[mg/kg/injection]; ordinates: cocaine injections earned (top), food reinforcers earned (center), %cocaine choice (bottom), per component. Group sizes: see Table 3; choice data for higher pretreatment doses may be a lower group size due to missing values, and are not shown when responding was reduced to the point that %choice could be calculated for fewer than two mice. *P<0.05, **P<0.01, ***P<0.001 vs. baseline, Bonferroni posttest following significant ANOVA; red asterisks refer to day 1, blue asterisks, to the chronic 1 week test.

Figure 5

Acute vs. chronic effects of continuously administered dopamine D_3-preferring ligands on concurrent cocaine self-administration and food-reinforced responding. Group sizes: see Table 3. Other details as in Figure 4.

Figure 6

Acute vs. chronic effects of continuously administered dopamine D_2-preferring or D_3-preferring ligands on total cocaine intake and total food reinforcers per session. Data shown are baseline, day 1 (2 hours of administration), and day 7 (one week of continuous administration). Abscissae: dose of pretreatment drug [mg/kg]; ordinates: total cocaine intake [mg/kg/session] (top) or total food reinforcers earned per session (bottom). Group sizes as in Table 3. *P<0.05, **P<0.01 Dunnett's multiple comparisons test vs. baseline following significant ANOVA.

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TABLES

Table 1. Classifications based on relative efficacies and affinities for dopamine D_2 or D_3 receptors determined *in vitro,* from published reports.

Ligand name	Classification	Binding selectivity (D_2-K_i / D_3-K_i)
NPA [a,b]	D_2/D_3 agonist	0.6-8
Terguride [c]	D_2/D_3 partial agonist	1.1
L-741,626 [d,e,g]	D_2-preferring antagonist	0.02 – 0.07
PD-128,907 [a,f]	D_3-preferring agonist	6.3-210
PF-592,379 [h, i]	D_3-selective agonist	>470
RGH-237 [j]	D_3-selective partial agonist	>1000
PG01037 [k]	D_3-selective antagonist	133

[a] Sautel et al., 1995

[b] Freedman et al., 1994

[c] Millan et al., 2002

[d] Kulagowski et al., 1996

[e] Millan et al., 2000

[f] Pugsley et al., 1995

[g] Caine et al., 2002

[h] Attkins et al., 2010

[i] Collins et al., 2012

[j] Gyertyan et al., 2007

[k] Grundt et al., 2005

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Table 2. Changes in cocaine choice A_{50} i.e., mg/kg/injection cocaine that produced 50% cocaine choices, acute administration experiment.

	Agonist (N)		Partial Agonist (N)		Antagonist (N)	
D2	**NPA**		**Terguride**		**L-741,626**	
	Vehicle (7)	0.18 [0.11 – 0.29]	Vehicle (7)	0.15 [0.11 – 0.21]	Vehicle (8)	0.21 [0.16 – 0.28]
	0.01 (5)	0.16 [0.09 – 0.27]	0.032 (4)	0.12 [0.06 – 0.26]	0.32 (8)	0.21 [0.15 – 0.27]
	0.032 (6)	0.06 [0.02 – 0.18]	0.10 (7)	0.15 [0.10 – 0.22]	1.0 (8)	0.29 [0.17 – 0.48]
	0.10 (6)	0.03 [0.02 – 0.08]*	0.32 (7)	0.14 [0.10 – 0.20]	3.2 (9)	0.44 [0.27 – 0.71]*
	0.32 (7)	0.03 [0.01 – 0.06]**	0.56 (6)	*not calculated*	5.6 (6)	*not calculated*
	0.56 (6)	0.03 [0.01 – 0.06]**	1.0 (6)	*not calculated*		
	1.0 (4)	0.04 [0.01 – 0.17]				
D3	**PD-128,907**		**RGH-237**		**PG01037**	
	Vehicle (11)	0.15 [0.11 – 0.19]	Vehicle (8)	0.21 [0.15 – 0.27]	Vehicle (6)	0.15 [0.11 – 0.21]
	0.10 (6)	0.19 [0.17 – 0.20]	10 (8)	0.11 [0.07 – 0.20]	1.0 (5)	0.22 [0.15 – 0.34]
	0.32 (7)	0.29 [0.15 – 0.57]	32 (8)	0.15 [0.07 – 0.30]	3.2 (8)	0.14 [0.06 – 0.33]
	1.0 (8)	0.21 [0.15 – 0.29]	56 (8)	0.24 [0.17 – 0.33]	10 (8)	0.14 [0.09 – 0.20]
	3.2 (8)	0.15 [0.05 – 0.44]			18 (6)	*not calculated*
	5.6 (6)	0.05 [0.01 – 0.14]*			32 (8)	*not calculated*

Values are group means, with 95% confidence limits indicated in brackets. N indicates group sizes.

Not calculated: responding was suppressed completely in more than half the animals, resulting in missing %choice values.

*P<0.05, **P<0.01 vs. vehicle (Dunnett's multiple comparisons test after significant ANOVA).

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Table 3. Changes in cocaine choice A_{50} [mg/kg/injection cocaine], chronic administration experiment

	Day 1	1 Week
NPA (N)		
Baseline (11)	0.06 [0.04 – 0.07]	–
0.00032 (6)	0.05 [0.03 – 0.08]	0.05 [0.03 – 0.08]
0.001 (6)	0.08 [0.04 – 0.17]	0.05 [0.03 – 0.08]
0.0032 (6)	0.04 [0.03 – 0.06]	0.04 [0.03 – 0.06]
0.01 (6)	0.05 [0.03 – 0.08]	0.03 [0.03 – 0.04]
L-741,626 (N)		
Baseline (15)	0.09 [0.07 – 0.10]	–
0.056 (6)	0.19 [0.11 – 0.32]**	0.08 [0.06 – 0.12]
0.18 (6)	0.14 [0.08 – 0.24]	0.10 [0.10 – 0.10]
0.32 (5)	0.08 [0.04 – 0.13]	0.05 [0.03 – 0.09]*
0.56 (4)	0.11 [0.10 – 0.13]	*not calculated*
PF-592,379 (N)		
Baseline (8)	0.07 [0.06 – 0.09]	–
0.56 (6)	0.10 [0.06 – 0.16]	0.07 [0.05 – 0.11]
1.8 (6)	0.07 [0.04 – 0.10]	0.05 [0.03 – 0.08]
3.2 (5)	0.06 [0.04 – 0.11]	0.03 [0.03 – 0.03]**
PG01037 (N)		
Baseline (21)	0.08 [0.06 – 0.10]	–
0.56 (6)	0.12 [0.08 – 0.19]	0.11 [0.05 – 0.24]
1.8 (6)	0.08 [0.06 – 0.12]	0.13 [0.04 – 0.39]
3.2 (6)	0.20 [0.11 – 0.38]**	0.15 [0.07 – 0.33]
5.6 (4)	0.07 [0.03 – 0.14]	*not calculated*

Data are group means with 95% confidence intervals in brackets. N indicates group sizes.

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*P<0.05, **P<0.01 vs. baseline (Dunnett's multiple comparisons test after significant ANOVA).

Not calculated: responding was suppressed completely in more than half the animals, resulting in missing %choice values.

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Table 4. Summary of present and previous findings

Classification	Ligand	Acute effects			Chronic effects		
		Cocaine intake	Food intake	Cocaine choice	Cocaine intake	Food intake	Cocaine choice
D2 agonist	NPA	↓	↓	↑	--	↓	(↑)
D2/D3 partial agonist	Terguride	--	↓	--			
D2 antagonist	L741,626	↑	↓	↓	--	↓	↑
D3 agonist	PD-128,907	--	↓	↑			
D3 agonist	PF-592,379				--	↓	↑
D3 partial agonist	RGH-237	--	(↓)	--			
D3 antagonist	PG01037	--	↓	-- or ↓	--	↓	--
D2/D3 partial agonist	Aripiprazole med. Dose [a]	(↓)	(↓)	↓	--	↓	--
D2/D3 partial agonist	Aripiprazole high dose [a]	(↑)	(↓)	--	(↑)	↓	(↑)
Monoamine reuptake inhibitor	D-amphetamine [b]	↓	↓	↑	(↓)	↑	↓

Effects refer to total cocaine intake per session, total food reinforcers per session, and percent cocaine choice, respectively.

↓: decrease, ↑: increase, --: no change; arrows in parentheses indicate trends that did not reach statistical significance.

[a] Thomsen et al., 2008

[b] Thomsen et al., 2013

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FIGURES

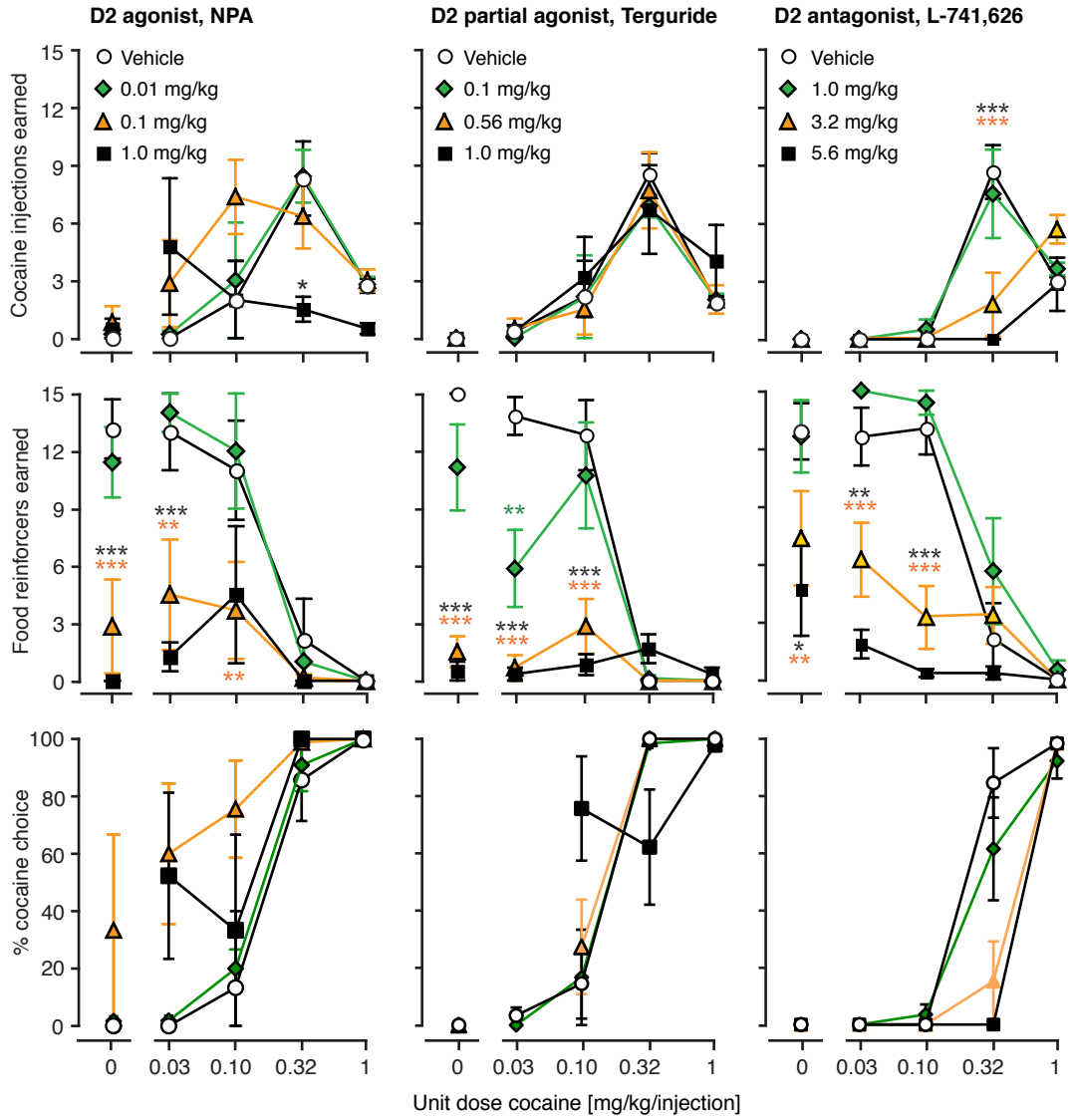

Figure 1

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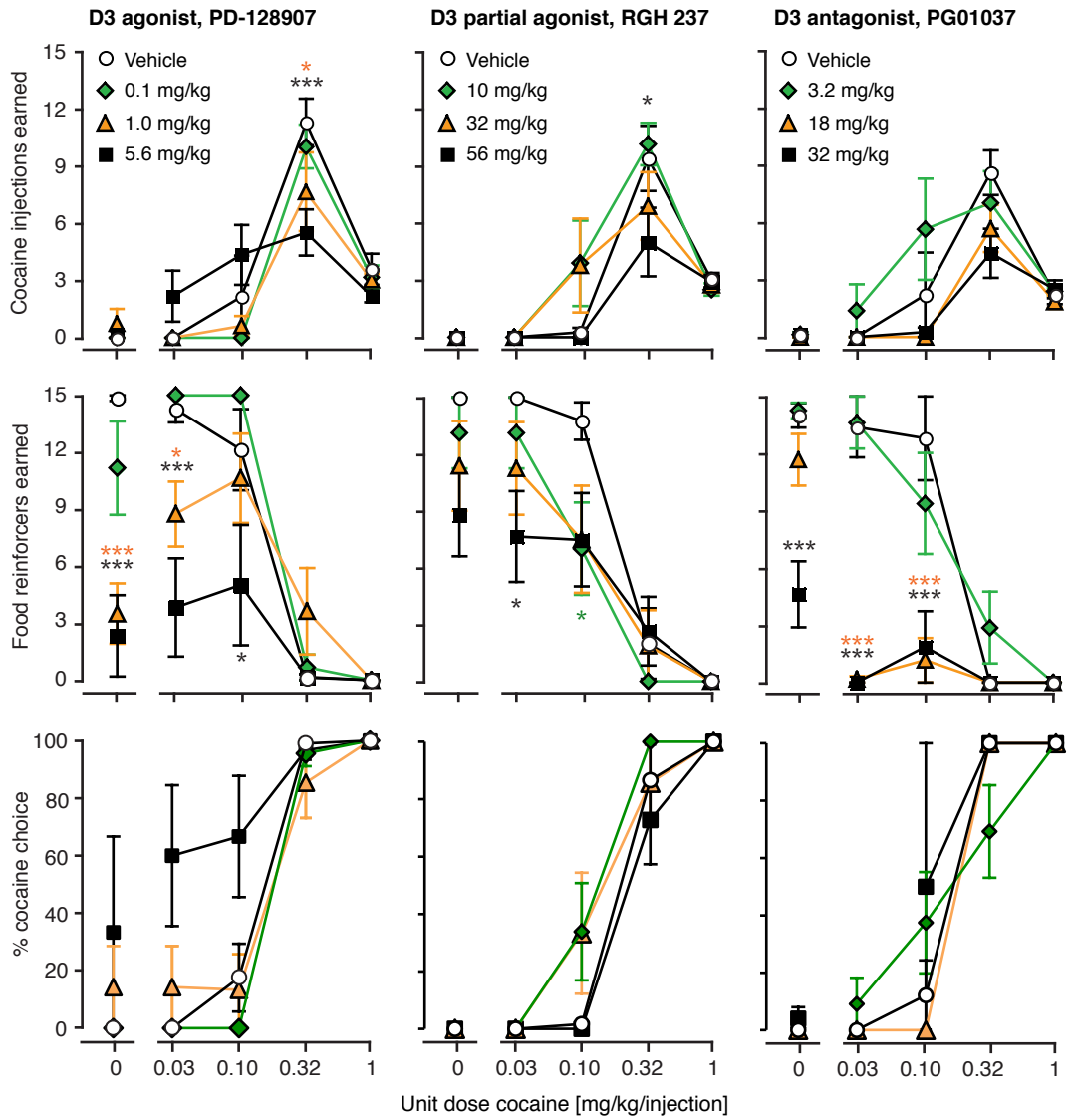

Figure 2

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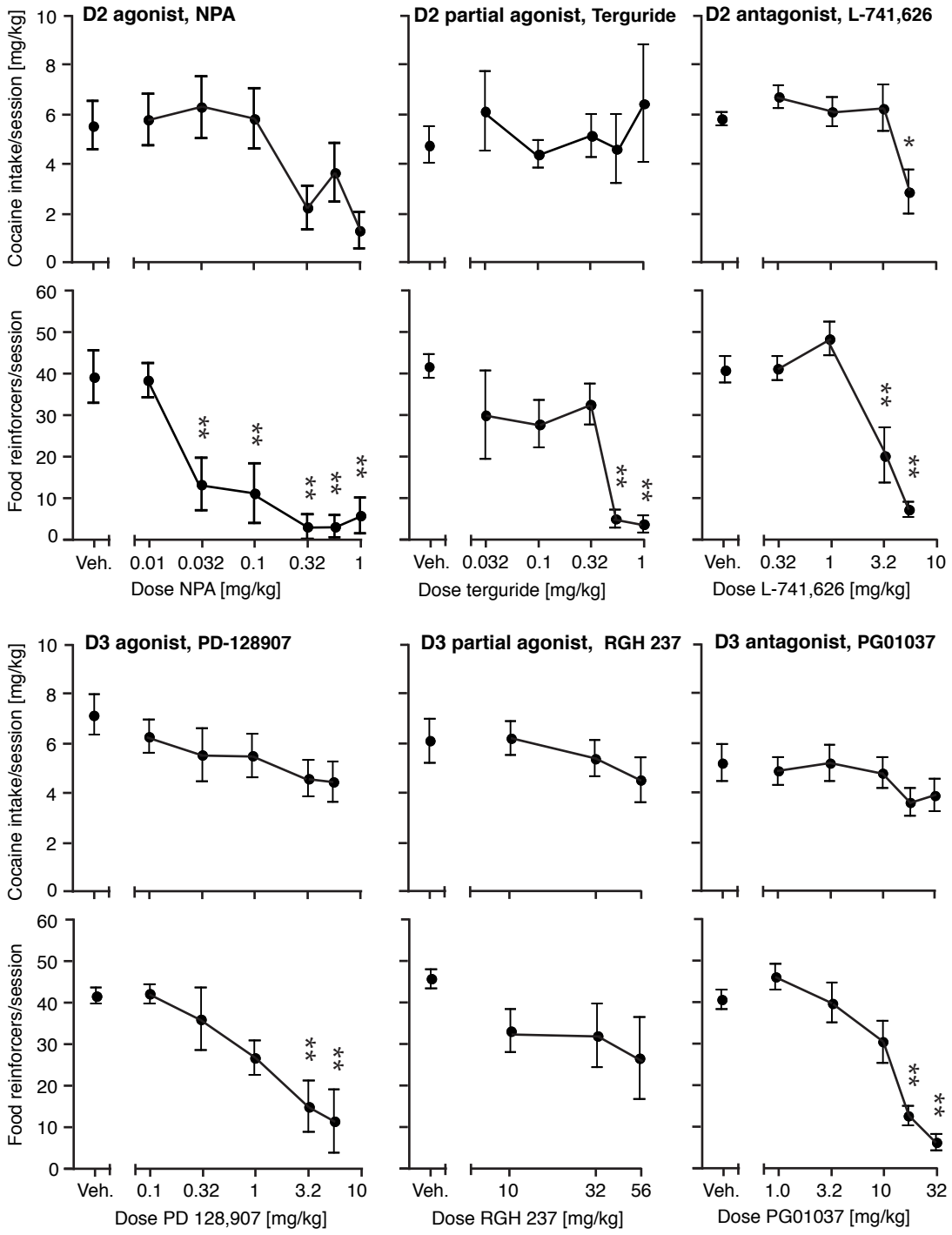

Figure 3

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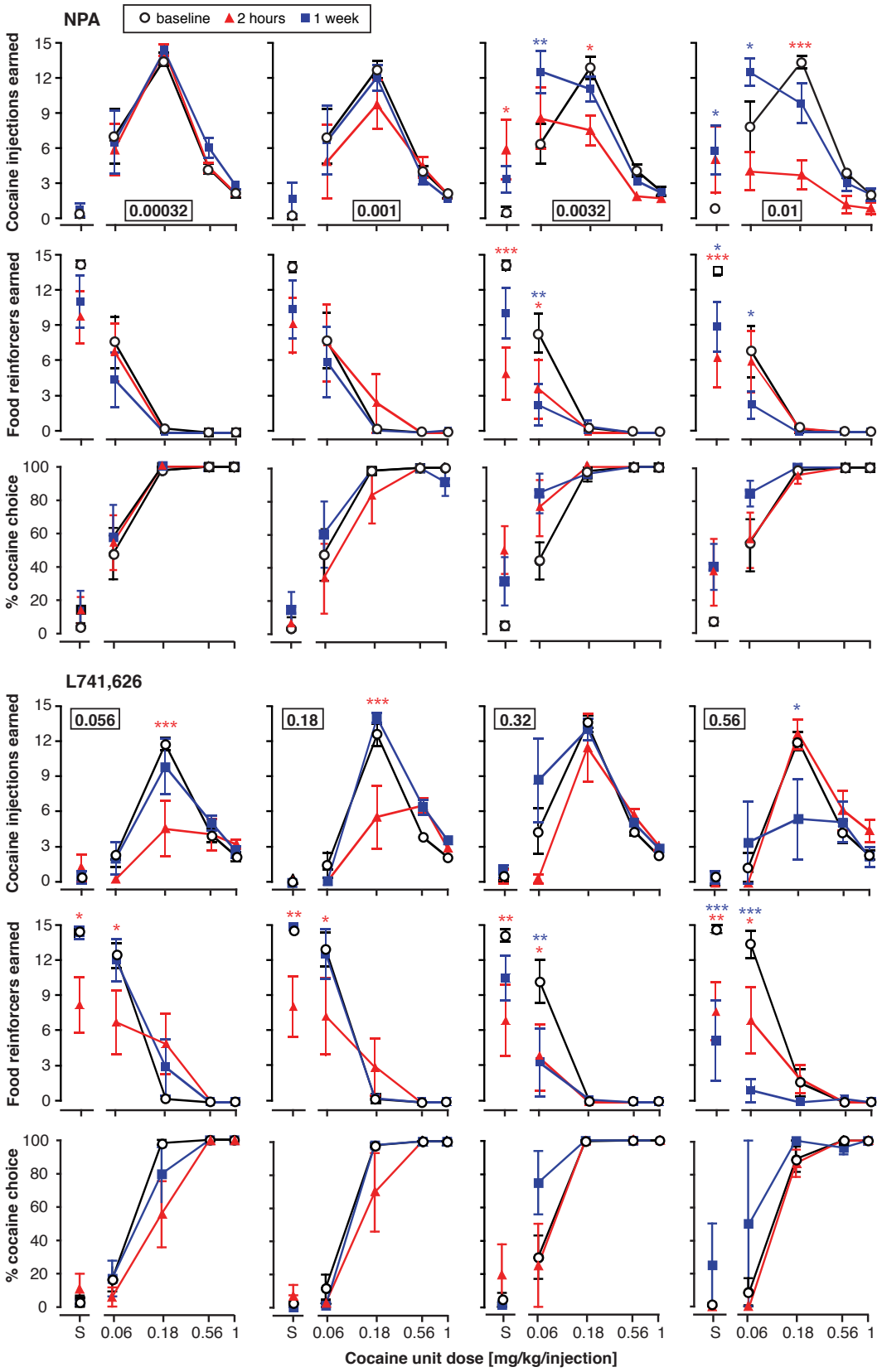

Figure 4

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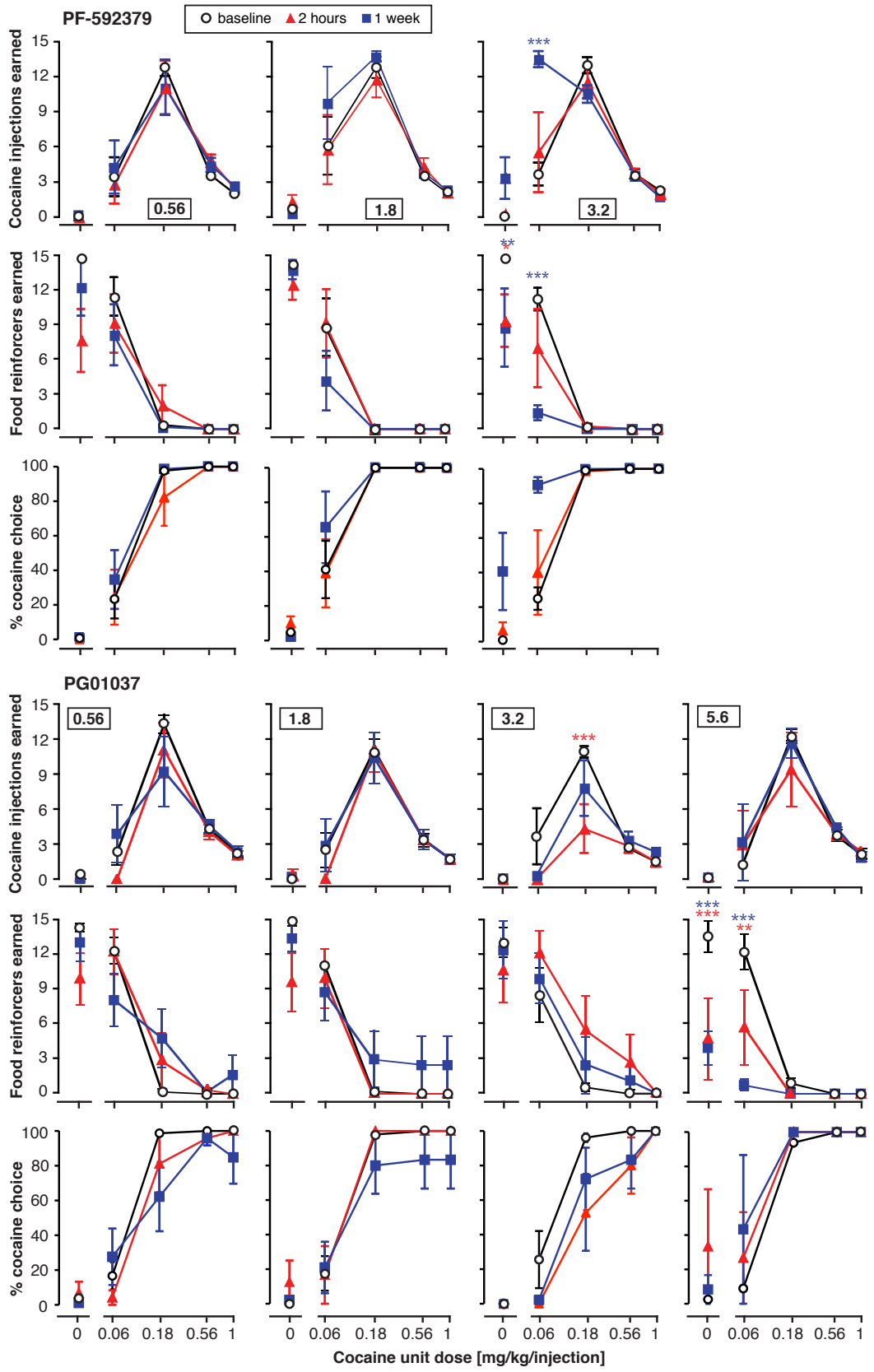

Figure 5

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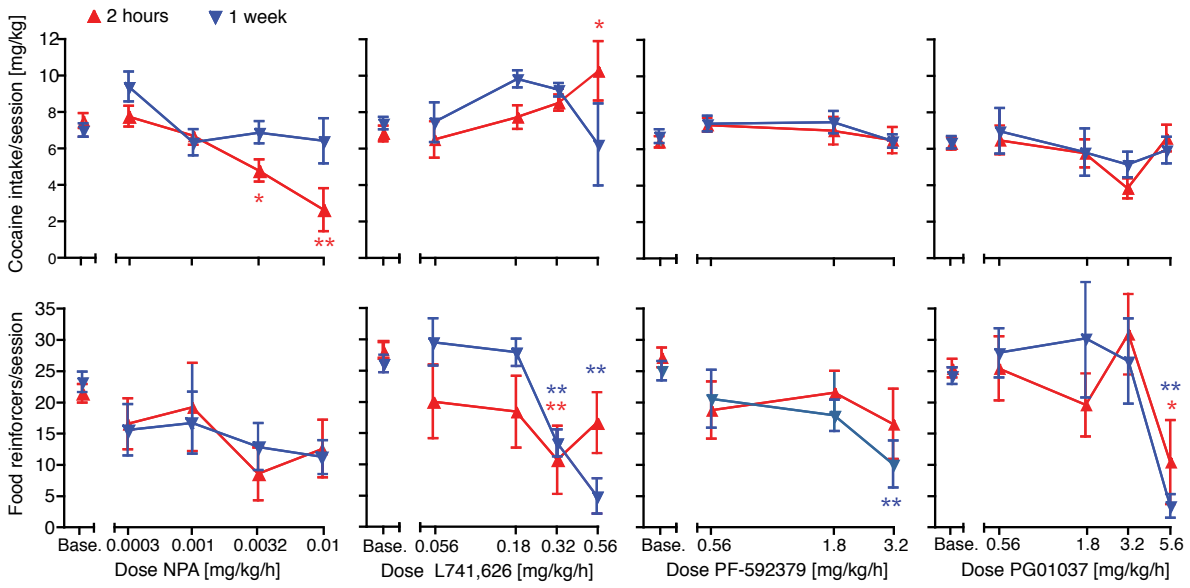

Figure 6