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Increased impulsive choice for saccharin during PCP withdrawal in female monkeys: influence of menstrual cycle phase

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Abstract

Background—In previous studies with male and female rhesus monkeys withdrawal of access to oral phencyclidine (PCP) self administration reduced responding for food under a high fixed-ratio (FR) schedule more in males than females and with a delay discounting (DD) task with saccharin (SACC) as the reinforcer. Impulsive choice for SACC increased during PCP withdrawal more than females.

Objectives—The goal of the present study was to examine the effect of PCP (0.25 or 0.5 mg/ml) withdrawal on impulsive choice for SACC in females during the follicular and luteal phases of the menstrual cycle.

Materials and methods—In Component 1 PCP and water were available from 2 drinking spouts for 1.5 h sessions under concurrent FR 16 schedules. In Component 2 a SACC solution was available for 45 min under a DD schedule. Monkeys had a choice of one immediate SACC delivery (0.6 ml) or 6 delayed SACC deliveries, and the delay was increased by 1 sec after a response on the delayed lever and decreased by 1 sec after a response on the immediate lever. There was then a 10-day water substitution phase, or PCP-withdrawal, that occurred during the mid-follicular phase (Days 7–11) or the late-luteal (Days 24–28) phase of the menstrual cycle. Access to PCP and concurrent water was then restored, and the PCP withdrawal procedure was repeated over several follicular and luteal menstrual phases.

Results—PCP deliveries were higher during the luteal vs the follicular phase. Impulsive choice was greater during the luteal (vs follicular) phase during withdrawal of the higher PCP concentration.

Conclusions—PCP withdrawal was associated with elevated impulsive choice for SACC, especially in the luteal (vs follicular) phase of the menstrual cycle in female monkeys.

Keywords

Delay discounting; follicular phase; impulsive choice; luteal phase; menstrual cycle; phencyclidine (PCP); rhesus monkeys; saccharin (SACC); withdrawal

Introduction

In a previous study we found when daily oral access to PCP was discontinued, impulsive responding for food on a delay discounting (DD) task increased in both males and females. This increased impulsive choice when PCP access was discontinued was used to infer a withdrawal effect due to physical dependence on PCP that was of greater magnitude in males than females (Carroll et al. 2009b). This is the only study we are aware of showing increased impulsive choice for another substance during drug withdrawal, and it may have

important implications for treatment of abstinent human drug abusers. That increased impulsive choice during drug withdrawal differs in males and females (Carroll et al. 2009b) suggests that withdrawal effects may be hormonally related and would vary with during phases of the menstrual cycle. While sex differences and hormonal effects have been well characterized during other phases of drug abuse (see Anker and Carroll 2012), there is little information about these factors in withdrawal effects. There is also little known about sex differences with PCP and other hallucinogens/dissociative anesthetics. In the epidemiological data PCP and hallucinogens are often combined, with no specific information about individual drug or whether there are sex differences in the use of these drugs (SAMHSA 2011). The goal of the present study was to compare PCP withdrawal effects on impulsive behavior for a nondrug reinforcer, saccharin (SACC) in female monkeys during the follicular and luteal phases of the menstrual cycle.

Oral PCP has been used in studies of withdrawal with monkeys because it is safely consumed in sufficient quantities with little chance of overdose; thus, withdrawal episodes can be safely repeated over time with no physical signs of distress. The results of withdrawal studies with PCP in monkeys (Carroll 1987, 1989; Carroll and Carmona 1991; Carroll et al. 1994; 2009b, Perry et al. 2006), are consistent with withdrawal studies in rats using other drugs (e.g., Barr and Phillips 1999; Corrigan et al. 1989; LeSage et al. 2006) generally reveal a suppression in behavior. For example, in most of the previous studies in which food-maintained behavior was maintained under high fixed-ratio (FR) schedules responding for food was reduced during drug withdrawal. In contrast, the present research showed consistent increases in responding for SACC under the DD schedule when highly preferred foods were used in a mouse paradigm, opiate withdrawal increased the motivation to eat under a PR schedule (Rouibi and Contarino 2012). Similarly, increased operant behavior for food in rats was reported during early opiate withdrawal (Cooper et al. 2010).

In the present study the drug withdrawal model used is a DD schedule with SACC as the reinforcer revealed that during PCP withdrawal, measures of impulsive choice for SACC significantly increased, more in males than females (Carroll et al. 2009b), while SACC intake was not changed. In that study a reverse condition was also found; food restriction (partial food withdrawal) increased impulsive choice for PCP self-administration under the DD schedule. Both PCP withdrawal and partial food withdrawal produced greater impulsive choice for another reinforcer, suggesting in general, that males are more responsive than females to loss of reinforcement associated with a change in schedule maintained by drug or food reinforcement. The greater withdrawal effect in males vs. females found with the impulsivity measures was similar to that previously reported for PCP withdrawal measured on a baseline of FR responding for food in male and female monkeys (Perry et al. 2006) and in withdrawal studies in which rats were injected with drugs such as ethanol, pentobarbital (Devau and Chadda 2001), morphine (Cicero et al. 2002; Suzuki et al. 1985), and methaqualone (Suzuki et al. 1988). The present use of an altered operant conditioning baseline as a measure of drug withdrawal effects is consistent with observational measures and further detects a mild form of physical dependence, lacking behavioral signs, that could result in relapse or substitution of another addictive substance.

The main goal of the present study was to extend the finding of increased impulsive choice for SACC during PCP withdrawal in males compared with females (Carroll et al. 2009b) to a comparison of withdrawal effects in females during the follicular vs luteal phase of the menstrual cycle. The follicular phase is characterized by higher estrogen, lower progesterone, while estrogen levels during the luteal phase can occasionally be equivalent to levels seen during the follicular phase, but with higher progesterone. Changes in withdrawal effects during different hormonal conditions may inform us on the optimal phase of the menstrual cycle for quitting drug abuse in women. For example, initial clinical studies on

menstrual phase and smoking cessation in women have reported that when behavioral therapy (Allen et al 2008) or behavioral therapy plus bupropion are used, a more favorable outcome occurs during the luteal phase (Mazure et al. 2011). In contrast, Franklin et al. (2007) and Carpenter et al. (2008) found better treatment results with agonist (nicotine replacement) therapy during the follicular vs luteal phase.

Phase of the menstrual cycle influences the subjective effects of drugs in humans and nonhuman primates (Evans and Foltin 2006, 2010; Hudson and Stamp 2011; Lynch and Sofuoglu 2010; Mello 2010). For example, self-report measures for smoked cocaine, such as liking, are greater during the follicular phase when estradiol levels are high than during the luteal phase when progesterone levels are elevated (Evans et al. 2002; Evans and Foltin 2006; Justice and de Wit 1999; Sofuoglu et al. 1999; White et al. 2002, but see Lukas et al 1996; Mendelson et al. 2001; Collins et al. 2007). However, no cycle effects were found with intranasal (Collins et al. 2007; Lukas et al. 1996) or i.v. cocaine (Mendelson et al. 2001). In a recent study smoked cocaine self-administration was compared during the follicular and luteal vs follicular phase when women were given micronized progesterone, and similar amounts of cocaine were self-administered under all 3 conditions (Reed et al. 2011). Mello et al (2007) reported increased progressive-ratio responding for cocaine during the follicular vs late luteal phase in cynomolgous monkeys. In contrast, we found a small increase in orally self-administered PCP during the luteal phase (compared with the follicular phase) in female rhesus monkeys (Newman et al. 2006). These differences in drug intake by phase could be due to effects of cocaine vs PCP.

Thus, another goal of the present research was to compare oral PCP self-administration (during baseline conditions) in female monkeys during the follicular and luteal phases. There have been very few studies of drug self-administration and drug withdrawal as a function of menstrual cycle phase in nonhuman primates. As in the previous study (Carroll et al. 2009b) PCP self-administration and withdrawal effects were evaluated in one component of the daily session, while impulsive choice on a delay discounting task for SACC (0.3% w/v) served as the measure of PCP withdrawal effects. We used two concentrations of PCP because previous results indicate more pronounced withdrawal effects that emerge at higher PCP concentrations or self-administered doses (Carroll et al. 2009b), but sex (Becker and Hu 2008; Lynch et al. 2002), and hormonal (Newman et al. 2006) differences are more likely to emerge at lower drug doses.

Material and methods

Animals

Seven adult female rhesus monkeys (*Macacca mulatta*) were used in a within-subjects experiment. The monkeys were previously trained to self-administer orally-delivered PCP under fixed ratio (FR) progressive-ratio (PR), and DD schedules (Carroll et al. 2009b). They were maintained at 85–90% of their free-feeding body weights that ranged from 5.5 to 10.0 kg, and they had unlimited access to water except during the time out periods 2 h prior to and 1.5 h after each daily session.

Monkeys were housed in individual home cages in quad formation (2-story, 2 side-by-side cages) in a room containing 12 monkeys. Each monkey's cage had an operant conditioning work panel mounted on a side wall that was used to record responses and dispense PCP, water, SACC and food. The monkeys were housed in a room that was temperature- (23°C) and humidity-controlled with the lights on from 0600 to 1800 h. Enrichment devices such as plastic toys, movies, and fruit and vegetables were available during the intersession period. The experiment was conducted in accordance with the Principles of Laboratory Animal Care (National Research Council 2011) and approved by the University of Minnesota Institutional

Care and Use Committee under Protocol Number 1007A85493. Laboratory facilities were accredited by the American Association for the Assessment and Accreditation of Laboratory Animal Care.

Apparatus

The quad cages used for both housing and testing were 83 cm wide, 76 cm high, and 100 cm deep (Lab Products, Maywood, NJ, USA). The operant conditioning panel mounted to the side of each cage contained 2 brass drinking spouts, 2 green stimulus lights above the drinking spouts, and a center red stimulus light indicated the start of a delay-discounting trial. The green light was steadily illuminated when water or saccharin were available, and it blinked when a drug solution was available above the drinking spouts. These devices were mounted on a panel that was attached to the outside of the cage with circular cut-outs in the cage wall allowing the lights and drinking spouts to protrude through the cage wall. The drinking devices were mounted within a circular clear Plexiglas plate that allowed the monkeys to see 4 stimulus lights mounted behind the plate. Two small white lights were illuminated when a lip contact response was made for water or SACC, and 2 small green lights indicated a lip contact for PCP. Med-PC software (Med-PC for Windows) and interfaces (Med Associates, St. Albans, VT, USA), located in an adjacent room were used to control the experiment and record data.

Procedure

The experimental design and procedures were similar to those reported by Newman et al. (2006, 2008) and Carroll et al. (2009b). There were 2 components in each day: Component 1- PCP self-administration under FR 16, and Component 2 - a DD schedule for SACC deliveries contingent on FR 8 lip-contact responses. This sequence was conducted 7 days a week as described below (See Table 1).

Experimental design

There were 4 conditions that were compared under PCP self-administration and withdrawal phases. 1) Water baseline (Wat-BL), 2) PCP available during luteal phase (PCP-L) or follicular phase (PCP-F), 3) The drug-available period immediately preceding PCP withdrawal (PCP Pre-WD), and 4) water substitution or withdrawal (Wat-WD) by substituting water for PCP. Menstrual cycle days 7–11 were used for the mid-follicular phase, and Days 24–28 for the late-luteal. The first part of the hyphenated abbreviation refers to liquid consumed during session – and the second is the menstrual phase (follicular or luteal) or the operational procedure, such as withdrawing PCP and replacing it with water (WD) or obtaining baseline measures with water available in both drinking spouts (Wat). Thus, PCP Pre-WD occurred during the early-follicular (Days 2–6) or mid-luteal (Days 19–23) phase. Condition 1, Wat-BL, was obtained once during the follicular and luteal phases, at a pre-experimental time when no drug withdrawal conditions had been tested for several months. The Wat-BL data were collected after several weeks of water access. The monkeys were stabilized on PCP, then water was substituted for several weeks to obtain a baseline for DD SACC without the influence of PCP or PCP withdrawal. The other 3 conditions (2–4) were repeated in order 2) PCP-F or PCP-L, 3) PCP Pre-WD, and 4) Wat-WD over several menstrual cycles to assess variability across repeated withdrawal episodes. Conditions 2–4 were not randomized because that is the sequence necessary to produce withdrawal effects and to study PCP intake during follicular and luteal phases. However, the 0.25 and 0.5 mg/ml PCP concentrations were tested in random order. The 3 repeated conditions were tested during the follicular and luteal menstrual cycle phases which were sampled in nonsystematic order. As Table 3 indicates, only 1 menstrual phase could be studied each month, and the entire procedure to test one menstrual cycle could last from over a month to up to 2 months.

Daily procedures

Component 1: PCP self-administration component—Monkeys were trained to self-administer PCP (0.25 mg/ml) and water under concurrent FR 16 schedules during daily 2-h sessions from 0945 to 1145 h (see Table 1), 7 days/week. Completion of the FR requirements for liquid deliveries on each of the 2 drinking spouts were independent of each other. Lip contact responses were counted on the two spouts, and when the FR was completed on a spout, liquid was delivered at that spout. PCP and water were available on alternating sides, each under a FR 16 schedule, with corresponding stimulus lights (PCP – flashing green, water – solid green) to signal the available liquid. All monkeys had previous experience with this schedule (Carroll et al. 2009b; Newman et al. 2006; Perry et al. 2006). This component was followed by a 30-min (1145–1215 h) when no food or liquid was available.

Component 2: Delay discounting saccharin component—This procedure has previously been described in detail (Carroll et al. 2009b), and the DD component occurred from 1215 to 1300 h (Table 1). Initially, there were 2 forced-choice trials to ensure sampling on the right and left side, and those were followed by 45 choice trials for up to 45 min. A SACC solution was available from both drinking spouts, small-immediate on one spout vs large-delayed on the other until 45 choice trials were completed or 45 min elapsed. Lip contacts on the drinking spouts, with a solid green light above each spout, were reinforced by a 0.6 ml delivery of SACC. On the “immediate” spout one delivery was contingent upon the completion of a FR 8 requirement for lip contacts and an additional FR 1 for 1 delivery of SACC. On the delayed side, after completion of FR 8, and then a FR 1 for each of 6 SACC deliveries were available. Following the SACC delivery on either spout the lights above the spouts were extinguished, and the center red light was illuminated to signal the next choice trial.

There was never a delay for the SACC delivery on the immediate spout; however, on the first day the first delivery on the delayed spout started at 10 sec. Subsequently, during the 45 choice trials each response on the delayed spout increased the delay by 1 sec, and each response on the immediate spout decreased the delay on the delayed spout by 1 sec. Thus, a delay was calculated after each SACC delivery for all 45 trials and averaged to yield a mean adjusted delay (MAD). On subsequent days the delay started where it left off on the previous day. Sides were reversed daily for the delayed and immediate spouts. The self-adjusting delay procedure has been used previously with rats (See review by Perry and Carroll 2008; Carroll et al. 2008, 2010) and monkeys (Carroll et al. 2009b, 2010), and MAD values have been used to indicate low (high MAD) or high (low MAD) impulsive choice for a substance.

PCP withdrawal conditions

Behavior was allowed to stabilize for at least 10 sessions (days) with PCP and water available during Component 1 (see Table 3). Subsequently PCP was replaced with water for 10 days. The 10-day PCP withdrawal period was based on previous findings that detected differences in PCP intake between follicular and luteal phases (Newman et al. 2006). The 10-day PCP withdrawal period was timed to occur during the mid-follicular (Days 7–11) or the late luteal phase (Days 24–28) of the menstrual cycle, allowing at least another 7 days back on PCP before another 10-day withdrawal period was implemented. Subsequently, the concurrent PCP and water condition was reinstated for 14–27 days until behavior stabilized (see Table 3).

Menstrual cycle phase determination

Menstrual cycle phase was determined by observation of menses onset and confirmation by examination of vaginal cytology. Monkeys were checked for bleeding each day, and vaginal swabbing was performed 1 h before the session 3 times per week. The method of Mauro et al. (1970) was used to classify cytology of the vaginal epithelium. Menses phase was defined by a predominance of parabasal and anucleated/cornified cell types. The follicular phase was described by superficial, intermediate, and anucleated/cornified cell types, and the luteal phase was indicated by the presence of parabasal, superficial, and intermediate and anucleated/cornified epithelial cells. Blood samples were not taken to obtain estradiol and progesterone levels because it would involve anesthetizing the animal and could result in behavioral disruptions the next day during a hormonal phase (follicular or luteal). We used bleeding to document the onset of menses, and swabbed the animals at least 5–6 days a week for vaginal cytology to confirm menstrual cycle status.

Drugs

PCP (phencyclidine HCl) was obtained from the National Institute on Drug Abuse (Research Triangle Institute, Research Triangle Park, NC). The PCP solutions were prepared with tap water, stored in a locked refrigerator, and placed in the reservoirs each day at room temperature.

Data Analysis

Within each PCP concentration 4 experimental conditions were compared: 1) baseline water (Water-BL) deliveries on both spouts during a pre-experimental extended period, 2) a baseline of PCP access that occurred during the follicular (PCP-F) or luteal phase (PCP-L) of the menstrual cycle, 3) a pre-PCP withdrawal (PCP Pre-WD) condition immediately before PCP withdrawal, and 4) the PCP withdrawal period (Water-WD) when water was substituted for PCP. These 4 conditions were compared in a 2-factor, repeated measures ANOVA with experimental phase and menstrual phase as the factors. Separate ANOVA were conducted for the 0.25 and 0.5 mg/ml PCP concentrations. Dependent measures such as PCP and water deliveries, mg/kg PCP intake, SACC deliveries, and the impulsive choice measure, mean adjusted delay (MAD), were compared within subjects for both the 0.25 and 0.5 mg/ml PCP concentrations, follicular and luteal phases, and across 4 repeated measures conditions. Data for each monkey consisted of a mean of the 4 days during the mid-follicular or late luteal phase when PCP was available or when PCP had been replaced with water for a 10-day withdrawal period. Means for the 4 days of each cycle were used for data analysis and presentation, as there were no increasing or decreasing trends in the daily patterns of intake over the 4 days. These data were then averaged over the 5–7 withdrawal periods and PCP self-administration periods that corresponded with each hormonal phase. Additional comparisons were made on liquid deliveries (PCP or water) during Component 1, and SACC deliveries and MAD scores during Component 2 across the 0.25 and 0.5 mg/ml concentrations during the PCP-F and PCP-L conditions. The mean data for each condition for the 7 monkeys were analyzed with repeated-measures analyses of variance (ANOVA; GB-Stat Dynamic Microsystems, Inc., Silver Spring, MD, USA). Additional two-condition comparisons were made using Fischers Least Significant Differences, Bonferroni-correlated t-tests. An overall significance level of $p < 0.05$ or $p < 0.05 \times \text{number of comparisons}$ for multiple comparisons, was observed.

Results

Figure 1 summarizes the results of withdrawing access to 0.25 mg/ml PCP during the follicular and luteal phases. The results (Fig 1a,b) show that PCP was consumed in excess of water during both the follicular and luteal phases ($F_{3,55} = 18.8802$, $p < 0.001$), indicating

that PCP was functioning as a reinforcer. Post hoc tests for both follicular and luteal phases indicated significant differences between Wat-BL and PCP-F, PCP-L, and PCP Pre-WD conditions ($p < 0.01$). The upper frames (Fig 1a,b) show the water and PCP liquid deliveries that were measured in the FR self-administration Component 1 over 4 experimental conditions: 1) water baseline (Wat-BL), 2) PCP availability during the follicular or luteal phases (PCP-F, PCP-L), 3) PCP intake immediately prior to the withdrawal phase (PCP Pre-WD), and 4) when PCP had been withdrawn and water was substituted for the drug (Wat-WD). Note that only the last 2 conditions (PCP-Pre-WD and Wat-WD) were conducted sequentially in time, the first 2 conditions were obtained as baseline measures once during the follicular and luteal phases before the experiment began (Wat-BL), or during several follicular or luteal phases (PCP-F, PCP-L) when PCP withdrawal was not taking place during that particular menstrual cycle phase.

Data shown in Fig 1c,d represent SACC deliveries earned during the DD Component 2. The SACC deliveries were not significantly different across the experimental conditions, indicating that changes in PCP or water intake during the preceding Component 1 (Fig 1a, b) did not affect SACC intake during the subsequent Component 2, nor did the availability of water or PCP during the 4 experimental conditions shown on the x-axis. Fig 1e,f shows the impulsive choice measure for SACC across the 4 experimental conditions.

There was a main effect of experimental condition ($F_{3,55} = 12.6672$, $p < .001$), and post-hoc tests indicated that MADs were significantly lower during PCP withdrawal (Wat-WD) than they were during the PCP-available condition immediately preceding withdrawal (PCP Pre-WD) for both the follicular (Fig 1e) and luteal (Fig 1f) phase indicating greater impulsive choice for SACC during PCP withdrawal. The MAD values are an average of their self-adjusted delays over the 45 choice trials per session were lower during water substitution or PCP withdrawal (Wat-WD) indicating higher impulsive choice for SACC (Fig 1e, f) compared with the PCP-available condition immediately preceding PCP withdrawal (PCP Pre-WD) during both the follicular (1e) and luteal (1f) phases.

Fig 2 shows similar mean ($\pm$ SEM) data for the 4 experimental conditions when 0.5 mg/ml PCP was available during phases shown on the x-axis label: 1) PCP-F and PCP-L phases, 3) PCP Pre-WD, and 4) Wat-WD. The results for 0.5 mg/ml PCP (Fig 2a, b) indicate that PCP deliveries exceeded those for water during the Component 1. In addition, PCP intake was higher during the luteal (Fig 2b) vs follicular phase (Fig 2a) in all 7 animals; however, this effect was significant only under the PCP access condition immediately prior to withdrawal (PCP Pre-WD) ($p < 0.05$) when the monkeys would have been in their mid-luteal phase. Statistical analyses indicated a main effect of experimental condition ($F_{3,55} = 5.8035$, $p < 0.05$), and menstrual phase ($F_{1,55} = 5.3033$, $p < 0.05$) on PCP deliveries. Post-hoc tests indicated that PCP was functioning as a reinforcer compared to the water baselines (Fig 2a, b), as there were significant differences between the water baseline - Wat-BL (F and L) and PCP-available (PCP-F and PCP-L) conditions, respectively ($P_s < 0.01$), as well as when water was substituted for PCP (PCP Pre-WD vs Wat-WD).

The SACC deliveries during Component 2 in the SACC available, follicular and luteal DD components (Fig 2c, d) did not differ significantly across experimental conditions within a menstrual phase, but SACC intake was higher in the luteal phase than the follicular phase ($F_{1,55} = 15.2147$, $p < 0.001$) during PCP-L vs PCP-F conditions and during the PCP Pre-WD condition immediately prior to PCP withdrawal ($P_s < 0.05$ and 0.01), respectively. Thus, both PCP (Fig 2b) and SACC (Fig 2d) intake increased during the luteal compared with the follicular phase.

The mean adjusted delay (MAD) values obtained in Component 2 and shown in Fig 2e and f, which serve as measures of impulsive choice, showed a similar pattern for withdrawal of 0.5 mg/ml PCP as previously reported for 0.5 mg/ml PCP (Fig 1). However, there were also menstrual cycle phase differences in MADs with 0.25 mg/ml PCP (Fig 2e, f). The MAD values (Fig 2e, f) for the SACC-reinforced DD task significantly varied by experimental condition ($F_{3,55} = 2.9906$, $p < 0.05$), and there was an experimental condition $\times$ menstrual phase interaction ($F_{3,55} = 10.6554$, $p < 0.05$). Lower MAD values (sec), indicating greater impulsive choice, during both follicular and luteal were found when comparing Wat-WD vs PCP Pre-WD, and PCP-F or PCP-L baselines ($p < 0.01$) and the Wat-BL water baselines in both follicular ($p < 0.05$) and luteal ($p < 0.05$, $p < 0.01$) phases (Fig 2e, f). The effect size of the difference in the impulsive choice measure during pre-withdrawal (PCP Pre-WD) vs withdrawal (Wat-WD) was 0.77 in the follicular phase and 0.51 in the luteal phase.

Table 4 shows that when PCP intake (mg/kg) was compared between the 0.25 mg/ml and 0.5 mg/ml concentrations, intake was significantly higher when 0.5 mg/ml (vs 0.25 mg/ml) PCP was available ($F_{1,27} = 11.2767$, $p < 0.01$), and post hoc tests of these comparisons revealed significant concentration differences under the PCP-F and PCP Pre-WD luteal conditions ($ps < 0.05$). However, Table 4 also shows that when adjusted for body weight the amount consumed during the PCP-F and PCP-L baselines or the PCP Pre-WD conditions, immediately before the F or L withdrawal periods, was not significantly different. This may have been due to small changes in body weight that occur over the menstrual cycle. In the present study body weights were obtained monthly and not synchronized with individual monkeys' menstrual cycles. Overall, the PCP concentration comparison indicates greater sensitivity of menstrual cycle phases (luteal $>$ follicular) for PCP and SACC intake at 0.5 mg/ml PCP, and the withdrawal-induced increases in impulsive choice for SACC were also greater at the 0.5 (vs 0.25 mg/ml) concentration.

Discussion

The results indicate that in female monkeys PCP withdrawal effects expressed as increased impulsive choice for SACC, are greater during the luteal (vs follicular) phase of the menstrual cycle; however, this may be a function of the higher PCP intake (mg/kg) in the luteal (vs follicular) phase. Greater withdrawal effects during the luteal phase is consistent with previous results showing enhanced withdrawal effects in males vs females using impulsive choice (Carroll et al. 2009) and other measures (Perry et al. 2006). Impulsive choice for SACC was greater when monkeys were maintained and withdrawn from the larger PCP concentration (0.5 mg/ml) compared with the 0.25 concentration in the present and previous (Carroll et al. 2009b) studies. Thus, higher baseline drug intakes are more likely than lower intakes to reveal withdrawal effects on an impulsive choice measure for SACC. The current results were consistent with those reported when both female and male monkeys tested in a similar procedure at the 0.5 mg/ml PCP concentration (Carroll et al. 2009b). In that study effect sizes were 1.5 in females and 1.6 in males compared with females in the current study with 0.77 in the follicular phase and 0.5 in the luteal phase. However, in the previous study with males and females.

The present and previous (Carroll et al. 2009b) results concur on the finding of increased impulsive choice for one substance during withdrawal of another substance and continue to emphasize that increased impulsive choice for a nondrug reinforcer is another dimension of drug withdrawal effects. In the present study impulsive choice for SACC was greater during Wat-WD compared with the pre-experimental water baseline (Wat-BL) condition (Fig 1e, 2e, f) suggesting that increased impulsive choice reflects a withdrawal effect than a difference in water vs PCP access in Component 1 on impulsive choice for SACC in Component 2.

That lowered MADs (higher impulsive choice) for SACC occurred during Wat-WD vs Wat-BL suggests that reduction in MAD is an acute response to PCP withdrawal.

While previous withdrawal effects were expressed as a decrease in behavior maintained by a high FR schedule for lab chow (e.g., Perry et al. 2006), the present and recent (Carroll et al. 2009b) finding of increased impulsive choice is consistent with animal work demonstrating increases in other behaviors such as intake of preferred foods (Rouibi and Contarino 2010; Cooper et al. 2010) or physical exercise (Miladi-Gorgi et al. 2011) during opiate withdrawal. A similar finding was reported by Giordano et al. (2002) in which cessation of one form of drug abuse led to impulsive behavior for another drug or excessive ingestion of preferred foods. However, opposite effects (increased anhedonia in a rodent model) were reported during withdrawal from chronic amphetamine exposure (Der-Avakian and Markou 2010). Studies of responding for natural rewards in drug-dependent, withdrawn human subjects show mixed results; reduced food intake in heroin dependent individuals (Lubman et al. 2009; Zijlstra et al. 2009), and increased craving or preference for liquid or solid sweets in opioid-dependent individuals (Morabia et al. 1989; Weiss 1982). Further work is needed to fully characterize this potential interchangeability between drug-seeking and impulsivity for nondrug reinforcers using parallel preclinical and clinical models. PCP withdrawal may have been altering behavioral economic systems (e.g., substitution of nondrug for drug reinforcers) that are associated with impulsivity for nondrug reinforcers. In future studies it would be useful to extend the withdrawal model to examine nondrug reinforcers that are more healthy than SACC or other sweet substances, such as physical exercise (e.g., Miladi-Gorgi et al. 2011). The findings from this animal work also suggest that humans encountering mild withdrawal effects leading to continued drug use, and impulsivity to resume drug use could be redirected to increase healthy behaviors.

One feature that is consistent across animal studies of withdrawal-induced suppression of operant conditioning behavioral baselines is that there was no observable evidence that mild PCP withdrawal produced malaise that may have been reflected by inactivity or anxiety/stress that might have been indicated by threats, or retreat that could explain the decreased responding under the high FR schedule for food (e.g., Perry et al. 2006). In the present study with visual observation it was impossible to distinguish the withdrawal phase from the drug-available phase. Furthermore, in previous PCP withdrawal studies using high FR schedules when monkeys were offered food from the experimenter or changed to a lower FR schedule for food, they readily consumed the food, while continuing to show a suppression in food-maintained responding at high FR schedules (Carroll and Carmona 1991). In the current study there was no change in daily food and water intake, body weight, or activity level during the baseline water (Wat-BL) or 3 repeated experimental phases. Thus, PCP withdrawal was not expressed as a physiological withdrawal syndrome. The present results are also consistent with previous findings that indicated elevated PCP self-administration during the late luteal phase compared with early or mid-follicular phase of the menstrual cycle (Newman et al. 2006). In the present study PCP deliveries were significantly higher during the luteal PCP Pre-WD baseline than during the Pre-WD baseline in the follicular phase at 0.5 mg/ml PCP (Fig 2c, d). However, PCP intakes (mg/kg) during the follicular and luteal phases were consistently but not significantly higher during the luteal vs follicular phase (Table 4). Similar PCP intakes were also reported in a previous PCP self-administration study in female monkeys using 0.25 mg/ml PCP (4.7 mg/kg) and 0.5 mg/ml PCP (9.2 mg/kg) where menstrual cycles were allowed to vary randomly (Perry et al. 2006) and to those reported for 0.25 and 0.5 mg/ml PCP in female monkeys during follicular and luteal phases (Newman et al. 2006).

The elevation in PCP intake during the luteal phase is in contrast to reports that the proestrus phase (higher estrogen) is related to elevated cocaine self-administration in rats (Anker and

Carroll 2010, Carroll et al. 2010) and the follicular phase (higher estrogen) in monkeys (Mello et al. 2011). Exogenously-administered estrogen is also associated with increased drug intake and positive effect of stimulant drugs seen in female vs male rats (Anker and Carroll 2010, 2011), but there is less known about the effect of ovarian hormones on self-administration of a variety of drug classes in nonhuman primates. There is also little known about the role of estrogen and progesterone on impulsivity for a drug reinforcer in rats or nonhuman primates. A recent study in female rats indicated that estradiol increased impulsivity for food in an effort-discounting task in rats to a greater extent in the ovariectomized (OVX) group compared with the pre-OVX or sham controls (Uban et al. 2012). The effect sizes (2–4) were larger than in the present monkey study, but it concurred with the present results that impulsivity for a nondrug reinforcer is subject to hormonal influences (Uban et al. 2012). Hormonal status, impulsivity, type of drug and pharmacological class of the self-administered drug are important factors to consider for treatment of drug abuse.

In humans fluctuations of estrogen and progesterone correspond with several differences in other physiological and subjective effects of stimulant drugs, particularly stimulants (Evans 2007; Terner and de Wit 2006). However, self-administration of other drugs of abuse such as alcohol (Freitag and Adesso 1993; Hay et al. 1984; Holdstock and de Wit 2000; Nyberg et al. 2004; Sutker et al. 1987), nicotine (Allen et al. 1999, 2004; Snively et al. 2000), marijuana (Lex et al. 1984), and opioids (e.g., Gear et al. 1996) does not vary as consistently with phase of the menstrual cycle in humans as does self administration of stimulants such as cocaine and methamphetamine (see review by Anker and Carroll 2011). Other drug classes may not have been studied extensively enough for a clear pattern of results to emerge, or they are not responsive to hormonal fluctuations over the menstrual cycle.

The present results focused on an impulsive-choice measure to assess drug withdrawal effects; however, varied reactivity to stress and craving during different menstrual cycle phases also varies consistently with stimulant abuse and withdrawal effects in humans, and overlap may exist between stress and impulsivity measures (Sinha 2008, Sinha et al. 2007). For example, the follicular phase women showed higher systolic/diastolic blood pressure measures, possibly related to stress, as they scored higher on self-report measures of anxiety and drug craving after exposure to stressful or drug-related stimuli than women in the mid-follicular phase (Sinha et al. 2007) when estrogen levels are highest. In contrast, the mid-luteal phase, was associated with high positive affective responses to cocaine and enhanced cue- and stress-induced cocaine craving. Thus, estrogen may facilitate both the positively reinforcing and aversive aspects of cocaine abuse in women depending on the stimulus that primes craving (e.g., cues, drug)..

In contrast, others have found no differences in the physiological and subjective responses to cocaine during different phases of the menstrual cycle (Lukas et al. 1996; Mendelson et al. 1999). Progesterone, the predominant hormone during the luteal phase, has opposite effects on subjective measures in women after stimulant administration, compared with estrogen. For example, women treated with progesterone showed a decrease in positive, subjective effects of smoked (Evans and Foltin 2006; Sofuoglu et al. 2002) and iv cocaine (Sofuoglu et al. 2004) compared with placebo-treated controls. High plasma levels of progesterone were associated with decreased craving after drug- or stress-related cues in cocaine-dependent women (Sinha et al. 2007). In the present study it is possible that elevated progesterone during the luteal phase alleviated the stress associated with PCP withdrawal and allowed impulsive choice for SACC to occur in the luteal phase compared to the follicular phase.

The implication for human females cycling through menstrual phases during chronic periods of drug use and abstinence is that vulnerability to relapse may vary with cycle phase. The

present results suggest that in impulsive behavior directed toward nondrug reinforcers peaks during the luteal phase of the menstrual cycle. An examination of withdrawal effects in humans, mainly focusing on smoking cessation, indicates that symptoms such as anxiety, depression, irritability, and poor concentration increased and are most severe during the luteal phase (Perkins et al. 2000; Pomerleau 1992). Cigarette craving in dependent women (Franklin et al. 2004), and cue-induced anxiety, physical stress responses, and cocaine craving (Sinha et al. 2007) are related to the late luteal phase. Furthermore, clinical work on smoking cessation during specific phases of the menstrual cycle indicated that the follicular phase (low progesterone) may be associated with more favorable outcomes when nicotine replacement therapy is used (Franklin et al. 2007; Carpenter et al. 2008). In contrast, quit attempts during the follicular phase (vs luteal) result in worse smoking cessation outcomes when behavioral strategies, or when non-nicotine (e.g., bupropion) or no medications are used to treat smoking cessation (Allen et al. 1999, 2004, 2008, 2009; Mazure et al. 2011). Thus, timing quit attempts to specific phases of the menstrual cycle as a function of the type of abused drug and treatment strategy is potentially important to a successful treatment outcome.

In summary, the present results indicated that withdrawal from PCP measured by elevated impulsive choice for SACC under a DD task was greater in female monkeys during the luteal than the follicular phase of the menstrual cycle. Thus, the risk of relapse to this form of drug abuse might be higher during the luteal phase and could lead to impulsive behavior directed toward another drug or nondrug substance. Once PCP access was restored, impulsive choice for SACC returned to lower levels indicating an acute and reversible effect of drug withdrawal. Females withdrawn from PCP were more at risk for these withdrawal effects in the luteal (vs follicular) phase of the menstrual cycle. The impact of drug withdrawal effects on impulsive choice for nondrug reinforcers may be important in designing treatment strategies that coordinate cessation attempts with the hormonal cycle. There may also be a benefit to directing impulsivity during withdrawal toward of healthy, alternative activities.

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Fig 1.

Mean ($\pm$ SEM) values are presented for seven female monkeys during the follicular phase (*left frames*) or luteal phase (*right frames*) of their menstrual cycle during four experimental conditions: water baseline (Wat-BL) with access only to water for an extended period, PCP access during the follicular (F) or luteal (L) phase (PCP-F or PCP-L), PCP (0.25 mg/ml) pre-withdrawal (PCP Pre-WD) immediately prior to withdrawal, and during withdrawal when water was substituted for PCP (wat-WD). The first term in the x-axis labels refers to the substance that was available for oral consumption during sessions, and the second term indicates baseline (BL) during the follicular (F) or luteal (L) phase or withdrawal (WD) of PCP. Frames a and b represent water or PCP deliveries earned under component 1 during the follicular and luteal phase of the menstrual cycle, respectively, when liquids were available under independent concurrent FR 8 schedules for 2 h. Frames c and d indicate the number of SACC deliveries, during the follicular (F) or luteal (L) phase, earned during component 2 under a delay-discounting task whereby the monkeys could earn one SACC delivery immediately under FR 8 or 6 deliveries after a delay, with the 1 or 6 deliveries each under an FR 8 schedule. Frames e and f depict the mean adjusted delay (MAD) calculated from the 45 choice trials under DD schedule during the follicular (F) or luteal (L) phase of the menstrual cycle, respectively. Significant differences across experimental conditions are

indicated by * ($p < 0.05$) and ** ($p < 0.01$), and significant differences between the follicular and luteal phases are indicated by # ($p < 0.05$), ## ($p < 0.01$).

Fig 2.

Fig 2 is the same as described for Fig 1 except the PCP concentration was 0.5 mg/ml. All other aspects of Fig 2 are as noted in Fig. 1.

Table 1

Timetable of daily procedures

8:00–9:45	Time out, no food or liquid
9:45–11:45	Component 1 drug and water concurrent FR 16 schedules
11:45–12:15	Time out, no food or liquid
12:15–13:00	Component 2 SACC delay discounting (45 min) FR 8 for each SACC delivery (immediate or delayed)
13:00–14:30	Time out, food, no liquid
14:30–8:00	Interession, only water available FR 1

Table 2

Menstrual phases studied for PCP baseline during follicular (PCP-F) and luteal (PCP-L) phases, PCP pre-withdrawal (Pre-WD), and PCP withdrawal (Wat-WD)

	0	4	8	12	16	20	24	28
Menses								
	PCP-F				PCP-L			
	Pre-WD		Wat-WD		Pre-WD		Wat-WD	
PCP BL	--PCP--				--PCP--			
PCP WD			<u>Water</u>				<u>Water</u>	

Table 3

Experimental design for PCP withdrawal
PCP and water availability for self-administration during Component 1 (9:45 am – 11:45 pm)

Baseline 10 days		Withdrawal 10 days		Recovery 14 – 27 days	
Spout 1	Spout 2	Spout 1	Spout 2	Spout 1	Spout 2
PCP FR 16.25, .5 mg/ml	H ₂ O FR 16	H ₂ O FR 16	H ₂ O FR 16	PCP FR 16.25, .5 mg/ml	H ₂ O FR 16

Mean ($\pm$ SEM) PCP intake adjusted for body weight (mg/kg) during PCP-F, PCP-L phases, and PCP Pre-WD baseline conditions before follicular (F – WD) or luteal (L – WD) phase PCP withdrawal and in a previous study of PCP self-administration using 3-h sessions (Newman et al. 2006) with 0.25 and 0.5 mg/ml PCP concentrations

Table 4

PCP concentration (mg/ml)	Menstrual phase		PCP Pre-WD baseline		Newman et al. 2006	
	PCP-F	PCP-L	Pre-F-WD	Pre-L-WD	F	L
0.25	4.4 *	4.8	4.5	5.5 *	4.0 *	4.8 *
0.5	6.3 *	6.7	6.1	7.2 *	6.0 *	6.6 *

* = 0.5 > 0.25 mg/kg intake (p < 0.05)