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Progesterone attenuates impulsive action in a Go/No-Go task for sucrose pellets in female and male rats

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Abstract

Impulsivity, or a tendency to act without anticipation of future consequences, is associated with drug abuse. Impulsivity is typically separated into two main measures, impulsive action and impulsive choice. Given the association of impulsivity and drug abuse, treatments that reduce impulsivity have been proposed as an effective method for countering drug addiction. Progesterone has emerged as a promising treatment, as it is associated with decreased addiction-related behaviors and impulsive action. The goal of the present study was to determine the effects of progesterone (PRO) on impulsive action for food: a Go/No-Go task. Female and male rats responded for sucrose pellets during a Go component when lever pressing was reinforced on a variable-interval 30-s schedule. During the alternate No-Go component, withholding a lever press was reinforced on a differential reinforcement of other (DRO) behavior 30-s schedule, where a lever press reset the DRO timer. Impulsive action was operationally defined as the inability to withhold a response during the No-Go component (i.e. the number of DRO resets). Once Go/No-Go behavior was stable, responding between rats treated with PRO (0.5 mg/kg) or vehicle was examined. Progesterone significantly decreased the total number of DRO resets in both males and females, but it did not affect VI responding for sucrose pellets. This suggests that PRO decreases motor impulsivity for sucrose pellets without affecting motivation for food. Thus, PRO may reduce motor impulsivity, a behavior underlying drug addiction.

Keywords

impulsivity; Go/No-Go; impulsive action; progesterone; sex differences; sucrose

Introduction

Drug abuse is a significant health problem in the United States, costing approximately \$193 billion annually (National Institute on Drug Abuse, 2015). Impulsivity, or a tendency to act without anticipation of future consequences, is a strong predictor of drug abuse and relapse (Weafer and de Wit, 2014; Perry and Carroll, 2008). Impulsivity contains two discriminable

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components: impulsive choice and impulsive action (Evenden, 1999). The present study focuses on impulsive action, which is commonly assessed using a continuous performance task (CPT; Rosvold et al., 1956), a two- or five-choice serial reaction time task (2- or 5-CSRTT; Carli et al., 1983) task, a stop signal reaction time (SSRT; Logan et al., 1997) task or a Go/No-Go task (Newman et al., 1985). In both human and animal studies, increased impulsive action on these tasks has been associated with drug use (Dalley et al., 2011; Dick et al., 2010; Diergaarde et al., 2008; Monterosso et al., 2005).

Current pharmacological treatments for drug abuse are relatively ineffective, and relapse rates for almost all drugs of abuse are consistently high (Volkow, 2011). One approach for reducing relapse and drug addiction in general is to treat the underlying mechanisms driving addiction such as anxiety, stress and impulsive behavior. The rationale for targeting underlying factors such as stress and impulsive behavior has been advanced by Solinas et al. (2010). Thus, the rationale for the present study was to test novel therapies, such as progesterone, that could potentially reduce underlying impulsive behavior which may influence subsequent drug-seeking.

Treatment development should also consider sex differences in impulsive action, as sex is an important variable in the development and treatment of drug abuse and impulsive behavior (see Weafer and DeWit, 2014 and Carroll and Lynch, 2016 for review). Male and female humans and non-human animals differentially responded to various motor impulsivity tasks (Weafer and de Wit, 2014). In humans, men committed more inhibitory errors (e.g. are more impulsive) in Go/No-Go and CPT tasks than women (Liu et al., 2013; Saunders et al., 2008); whereas, women had more inhibitory errors and longer reaction times in a SSRT paradigm than men (Morgan et al., 2011; Crosbie et al., 2013; but see Fields et al., 2009). In contrast, others have reported no sex differences in impulsive action (Townshend and Duka, 2005; Fernie et al., 2010; Reynolds et al., 2006).

In animal laboratory studies, female rats made more premature errors and overall responses in the 2-CSRTT (Burton and Fletcher, 2012) and a Go/No-Go task for cocaine (Anker et al., 2008) than males, suggesting that motor impulsivity was higher in females than males. This may have been task-specific, as male rats showed greater impulsive action (i.e., premature responses) on a 5-CSRTT than females (Bayless et al., 2012; Jentsch and Taylor, 2003; Papaleo et al., 2012). In other studies, no sex differences were reported on impulsive action with rats (Anker et al., 2008) and mice (Papaleo et al., 2012) on the Go/No-Go and 5-CSRTT tasks, respectively. Collectively, these findings were mixed, but if tasks in which inhibition of an inappropriate response is considered as the measure of impulsive action (i.e., CPT, 5-CSRTT and Go/No-Go task), then males typically displayed greater impulsive action than females.

These mixed sex differences in models of impulsivity may be due to fluctuating hormonal levels. Female gonadal hormones, such as estradiol and progesterone (PRO), influence risk-taking behavior (Sukolova and Sarmany-Schuller, 2011; Chavanne and Gallup, 1998; Derntl et al., 2014), and higher levels of estradiol were related to greater impulsivity in the SSRT (Colzato et al., 2010). In animal research, the impact of gonadal hormones on impulsivity has been even less thoroughly examined. Bayless et al. (2012) tested females only during the

proestrous phase of the estrous cycle, when estradiol is high, and they found that males made more premature responses than females under challenging conditions. Age- and difficulty-dependent effects of estradiol on ovariectomized female rats in the 5-CSRTT were also shown (Bohacek and Daniel, 2010). However, the effects of female gonadal hormones such as estradiol have not been thoroughly examined on direct measures of impulsive action and the impact of PRO in these tasks in rodents is currently unknown.

In contrast, the actions of estradiol and PRO on drug-seeking behavior are becoming better understood (see Carroll and Smethells, 2016; Carroll and Lynch, 2016 for review). Overall, estrogen is associated with increased drug abuse, while PRO and its metabolites are related to reductions in addiction-related behaviors such as relapse and escalation (Anker and Carroll, 2010). Progesterone is a female gonadal hormone that is used in contraceptives and in drugs used to maintain pregnancies (Jones et al., 2012). Exogenously-delivered PRO is effective for treating stimulant abuse in animals (Anker et al., 2009; Zlebnik et al., 2014; Evans and Foltin, 2010) and may have potential as a stimulant cessation agent in humans (Fox et al., 2013; Evans and Foltin, 2006; for review, see Quinones-Jenab and Jenab, 2010; Evans and Foltin, 2010; Carroll and Lynch, 2016; Carroll and Smethells, 2016). A recent report indicated that PRO and its metabolites (allopregnanalone) reduce stress and impulsive behavior as measured by the Stroop test in humans (Milivojevic et al., 2016). However, the effect of PRO on treating underlying behaviors such as impulsive action that have been implicated in drug abuse in rats is currently unknown.

Thus, the goal of the present study was to examine the effects of exogenous PRO on impulsive action in a Go/No-Go task for food (i.e. sucrose pellets). Responding during the Go phase was reinforced, while responding during the No-Go phase was punished with a delay to food imposed by resetting a differential reinforcement of other (DRO) behavior schedule (e.g. a DRO reset) which led to a delay in reinforcement. The number of DRO resets is considered a measure of motor impulsivity (Winstanley, 2011). It was hypothesized that male rats would behave more impulsively (e.g., increased DRO resets), given that they display greater impulsive action on related tasks than females (e.g., 5-CSRTT; see Weafer and de Wit, 2004). Conversely, it was hypothesized that PRO would decrease impulsive action to a greater extent in females than males based on findings that females showed greater response to the effects of PRO on drug-seeking than males (Anker et al., 2009; Zlebnik et al., 2014; Fox et al., 2013; Evans and Foltin, 2006; for review, see Quinones-Jenab and Jenab, 2010).

Materials and Methods

Subjects

Twenty adult female and 20 male Wistar rats (Harlan Inc., Indianapolis, IN, USA), weighing 200–224 and 250–274 g, respectively, at arrival were used as subjects. Males and females were matched for age. Rats were initially pair-housed in plastic home cages with ad libitum access to water and food (Teklad 2018, Harlan Laboratories, Madison, WI, USA). After the experiment began, rats were continuously housed in the experimental chambers described below (see apparatus) in rooms maintained at 24° C and 40–50% humidity with a 12h on/12h off light cycle (lights on at 600).

Rats had *ad libitum* access to water during the experiments, but food was limited to 20 g (male) and 16 g (female) of chow (Teklad 2018, Madison, WI) per day, provided 4 hr post-session. The amount of sucrose pellets (Bioserv F0021, Frenchtown, NJ) consumed during the experimental session was subtracted from the daily feeding ration to ensure adherence to reduced food rations. All experiments were approved by the University of Minnesota Institutional Care and Use Committee (protocol #1307-30762A), and facilities were accredited by the American Association for the Accreditation of Laboratory Animal Care. All experiments were performed in compliance with the Guide for the Care and Use of Animals (National Research Council, 2011).

Apparatus

The apparatus consisted of customized octagonal chambers with alternating Plexiglas and stainless steel walls. The chambers contained two retractable levers mounted approximately 4 cm above the floor of the chamber, and each was equipped with tri-colored stimulus lights (4.6 W) centered directly above each lever. During the experimental sessions, 45 mg sucrose pellets were delivered to a trough by a pellet feeder (H14-23R, Coulbourn Instruments, Whitehall, PA). An overhead white houselight (4.6 W) provided general illumination within the chambers when sessions were ongoing. Each chamber was enclosed in a sound-attenuating wooden box with a small ventilation fan. The experimental sessions and data recording were controlled by a computer running Med-PC IV® software (Med Associates, St. Albans, VT, USA).

Drugs

Progesterone was dissolved (0.625 mg/ml) in peanut oil (Sigma Aldrich, St. Louis, MO). Progesterone (0.5 mg/kg) or the corresponding vehicle (e.g. peanut oil) was administered subcutaneously 30 min prior to session during the treatment phase at an endogenously relevant dose according to previous methods used previously to reduce cocaine reinstatement (Anker et al., 2007; White and Uphouse, 2004).

Experimental Design

Rats were initially trained to lever-press for a sucrose pellet using an autoshaping procedure. At the beginning of the 1-hr session, the house light was turned on, and the retractable levers were presented. For the first 5 days, pellets were delivered on a variable time (VT) schedule, starting on a VT60 sec, and the delay escalated over each subsequent day (e.g. 60, 120, 240, 480, and 960). During this autoshaping period, pellets were also available on a fixed ratio (FR) 1 schedule, with responses on both levers resulting in one pellet delivery. Autoshaping continued until rats met the criteria of 2 days of 30 or more earned pellets at the final VT960 schedule (i.e. 30+ responses on either lever).

After rats met criteria, they were transferred to the Go/No-Go program. This program consisted of 2 hr of alternating Go and No-Go components with a 5 sec timeout in between components. The Go component lasted 15 min, while the No-Go component lasted 5 min, and the No-Go component always followed the Go component (and vice versa). Rats were randomly assigned to an active lever that produced a pellet when pressed, and an inactive lever that, when pressed, had no consequence.

The Go component was marked by illumination of a stimulus light over the assigned active lever. During the Go component, rats could lever-press on the active lever to receive a sucrose pellet on a variable interval (VI) 30 sec schedule. Responses during the Go component are termed VI responses. The No-Go component was signaled by a flashing light over the active lever. During the No-Go component, withholding a response on the active lever produced a pellet under a DRO 30-sec schedule. If a rat made a response on the active lever during this phase, the DRO timer was reset to zero and a DRO reset was recorded.

Once VI responding and DRO resets stabilized, defined as 3 days with responding within 20% variation of the previous day's level and no downward trend, rats were moved to the treatment phase. In this initial phase (e.g. pre-treatment), animals took between 6 and 34 days to reach stability (mean=15±2.21). During treatment, rats were randomly assigned to receive either PRO (0.5 mg/kg) or VEH 30 min prior to the session. Responses during the Go and No-Go components were measured until stable responding was again reached. Treatment was continued daily, 7 days per week, until stability criteria were met. Days to stability criteria ranged from 5 to 16 days across rats (mean=10.2±0.83).

Statistics

All data are expressed as mean ± standard error of the mean (SEM). The first three days of stable behavior as defined above were used to examine both the DRO resets and VI responding during the pre-treatment and treatment phases. To examine changes in responding after treatment, raw data from each rat was transformed into percent change from their baseline mean. Percent change was used to normalize the data, as there was a high degree of variability in VI responding and resets between rats. To conduct statistical analyses, the percent change was averaged over the 3 days of stable responding. Sex differences during the go component were analyzed with independent samples t-tests. The effects of sex and treatment were analyzed in a two-way ANOVA. Further analyses using Bonferroni *post hoc* tests were used to examine percent change in responding from baseline after treatment. Means are reported as ± SEM, and an alpha value of 0.05 was used to assign statistical significance. Cohen's *d* were calculated for t-tests and *post hoc* analyses and eta squared were calculated for ANOVA to examine effect sizes using online statistical software. Statistical analyses were conducted with GraphPad Prism version 5.0.

Results

Results of an independent samples t-test indicated no significant differences between males and females on average response rates (see Table 1) during the Go component ($p>0.05$, $d=1.25$). There was no significant difference between males and females on DRO resets during baseline ($p>0.05$, $d=0.24$), suggesting that during the baseline component, male and female rats did not significantly differ in the Go/No-Go measure of impulsivity. Table 1 shows the baseline values of DRO resets.

Figure 1a illustrates stable responding during the 3-day baseline and treatment in both treatment groups in males, while Figure 1b illustrates responding in females. A two-way ANOVA on percent change of DRO resets during the No-Go component showed a significant main effect of treatment [$F(1,36)=2.90$, $p<0.001$, $\eta^2=0.33$], but there was no main

effect of sex and no interaction ($p>0.05$, $\eta^2<0.02$). *Post hoc* analyses revealed a significant change in baseline after PRO vs. VEH treatment in both males ($d=1.67$) and females ($d=1.30$, $p<0.05$), as progesterone significantly decreased DRO resets during the No-Go component, while VEH did not.

Figure 2 shows VI responding during 3 days of stability in males and females, respectively. A two-way ANOVA on VI responding during the Go component showed no significant main effect of treatment or sex and no interaction ($p>0.05$, $\eta^2<0.09$). Table 1 summarizes the baseline values of responding. Progesterone and VEH treatment did not affect responding for food in males or females.

Discussion

The present results showed that PRO, a female gonadal hormone, attenuated impulsive action (i.e., DRO resets) for sucrose pellets in both male and female rats during the No-Go component of the schedule. However, PRO did not change responding for sucrose pellets during the GO component, suggesting that the treatment specifically targeted impulsive action without altering food-maintained behavior. Targeting the underlying behaviors associated with drug addiction, such as impulsivity, is a potential avenue for treating drug abuse (Solinas et al., 2010), and these results suggest that PRO should be further examined as a treatment for maladaptive, impulsive behaviors in both male and female rats, specifically in relation to subsequent drug use.

This study is the first to show that exogenously administered PRO decreases impulsive action in rats. A recent study in humans by Milivojevic et al. (2016) showed similar results, as allopregnanalone, a metabolite of progesterone, improved Stroop performance, a measure related to impulsive action. However, the beneficial effects of PRO may be specific to this particular subtype of impulsivity, as recent evidence from our laboratory showed no effect of PRO on impulsive choice for sucrose pellets in females and males, measured by a delay discounting task (Smethells et al., 2016). A cross-species study with rats and humans indicated that measures of impulsive action and impulsive choice were not directly correlated (Broos et al., 2012), and this was similar to other findings in human and non-human animals (Reynolds et al., 2006; Dougherty et al., 2009; Reynolds et al., 2008; Winstanley et al., 2004; but see Robinson et al., 2009). Additionally, impulsive choice and impulsive action were differentially affected by pharmacological challenges with amphetamine and atomoxetine (Broos et al., 2012). Broos et al. (2012) suggested that treatment approaches should take into account the multifaceted nature of impulsivity in designing and implementing treatment strategies. Initial findings of attenuated motor impulsivity in the present study after PRO treatment compared to the lack of effects of PRO in the delay-discounting task in rats in Smethells et al. (2016) suggest that PRO may be more successful in treating impulsive action than impulsive choice. However, further work with these impulsivity models is needed.

A potential alternative explanation for the decrease in impulsive action for sucrose is that its reinforcing value was attenuated by PRO, as PRO reduced the reinforcing efficacy of cocaine (Larson et al., 2007; Mello et al., 2007). However, since VI response rates were not

altered following treatment, it seems unlikely that the change in impulsive action was due to direct effects on the reinforcing efficacy of food. While the data suggests that the attenuation of impulsive action is not due to a change in reinforcement, the mechanism behind this reduction in impulsivity is currently unknown. Much of the research on PRO's effects on drug-seeking suggest a role for allopregnanalone (ALLO), a metabolite of PRO (see Carroll and Anker, 2010 for review). Allopregnanalone is a positive modulator of GABA receptors and PRO facilitates GABA transmission (for review, see Barth et al., 2015), a system that has been implicated in impulsive behavior in both humans and animals (Lee et al., 2009; Jupp et al., 2013; Murphy et al., 2012). However, whether the interaction of PRO and its metabolites with the GABA system play a role in the attenuation of impulsive action in male and female rats such as the effects seen in this experiment remains to be studied.

The finding that female and male rats had comparable baselines of impulsive action in a Go/No-Go task was similar to the previous reports on the topic. Milivojevic et al. (2016) showed no sex differences in a measure of inhibitory control in humans. Anker et al. (2008) also reported similar baseline rates of responding across males and females in impulsive action for sucrose pellets using a modified (i.e., extinction) No-Go component. Anker and colleagues reported greater impulsive action for cocaine infusions in females than males; however, these inconsistencies could be explained by differences in the reinforcing value and neurobiological effects of food vs. drugs.

Previous reviews of the impulsivity literature indicate that sex differences in impulsive action are inconsistent (see Weafer and de Wit, 2014), and phase of estrous cycle may play a role (see Colzato et al., 2010). We did not find sex differences between males and females on either DRO resets during the No-Go component or responding during the Go component in this measure of impulsive action, potentially due to the cycling differences in female rats that may have reduced any potential sex-specific effects. However, responding was averaged over a period of 3 consecutive days, which would minimize any variability in responding due to the phase of the hormonal cycle in females, as each cycle lasts approximately 4 days (Marcondes, 2002).

Both males and females showed similar attenuation of impulsive action after PRO administration. This finding was unexpected given previous work indicating that females were relatively more responsive than males to exogenous PRO treatment on drug-seeking measures (Anker et al., 2009; Zlebnik et al., 2014; Fox et al., 2013; Evans and Foltin, 2006; for review, see Quinones-Jenab and Jenab, 2010). The significant decrease in motor impulsivity produced by PRO in both males and females suggested that this treatment could function as a broad treatment across genders. Given the relationship between impulsive action and drug abuse (see Perry and Carroll, 2008), future research on the mechanisms by which PRO exerts its effects, either on the maladaptive behaviors underlying drug abuse, or drug-seeking, are necessary to determine the most successful treatment measures for drug use.

In conclusion, PRO decreased impulsive action in rats for sucrose measured by DRO resets during a Go/No-Go task. However, PRO did not decrease general VI responding for food, suggesting that it did not diminish the reinforcing efficacy of sucrose pellets. While females

were more sensitive to the therapeutic effects of PRO on drug-seeking, PRO decreased impulsive action equally in both male and female rats in this study. Overall, results suggest that PRO decrease impulsive action in rats and promotes the need for further research on the use of PRO in treating impulsivity, a maladaptive behavior that may underlie drug addiction in humans.

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Highlights

- Progesterone decreased impulsive action for food in a Go/No-Go task in rats.
- Progesterone did not decrease motivation for food.
- Progesterone decreased impulsive action equally in both male and female rats.

Figure 1.

DRO resets during the No-Go phase expressed as percent of average responding ($\pm$ SEM) for sucrose pellets during the 3 sessions of stable responding in (a) males and (b) females. The bar with an asterisk shows a significant difference in responding between the PRO (n=10) and VEH treated (n=10) groups. * = $p < 0.05$.

Figure 2.

VI responding during the Go phase expressed as percent of average responding ($\pm$ SEM) for sucrose pellets during the 3 sessions of stable responding in (a) males and (b) females. There were no significant differences after treatment in either the PRO or VEH groups.

Table 1

Mean ($\pm$ SEM) total responses during the Go phase shown by VI responding and the No-Go phase shown by DRO resets in males and females during pre-treatment (Pre-Tx) and treatment (Tx).

	DRO Resets Males	DRO Resets Females	VI Responses Males	VI Responses Females
Pre-Tx	87.7 ($\pm$ 17.0)	112.2 ($\pm$ 33.8)	126.8 ($\pm$ 7.9)	104.8 ($\pm$ 7.9)
Tx	63.4 ($\pm$ 12.5)	37.1 ($\pm$ 10.8)	127.7 ($\pm$ 5.3)	93.3 ($\pm$ 4.5)