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Methylphenidate and fluphenazine, but not amphetamine, differentially affect impulsive choice in Spontaneously Hypertensive, Wistar-Kyoto and Sprague-Dawley rats

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Abstract

Impulsivity is one of the core symptoms of attention-deficit/hyperactivity disorder (ADHD). The spontaneously hypertensive rat (SHR), a putative animal model of ADHD, has been used to investigate the neurobiology of impulsivity, although this model has been questioned over concerns that use of Wistar-Kyoto rats (WKY) as a comparison strain may exaggerate effects. The present study compared SHR, WKY and standard, outbred Sprague-Dawley (SD) rats on a delay discounting task where the primary measure was mean adjusted delay (MAD), or the indifference point (in sec) between choice of a immediate delivery of 1 grain-based pellet versus 3 pellets delivered after varying delays. The acute dose effects of the ADHD medications amphetamine (0.1–1.0 mg/kg) and methylphenidate (1.0–10 mg/kg) were then determined; in addition, the effect of the dopamine receptor antagonist fluphenazine (0.1–1.0 mg/kg) was also assessed for comparison with the indirect agonists. While there were no strain differences in the rate of task acquisition or stabilization of baseline MAD scores, SHR had significantly lower MAD scores than WKY but not SD due to the greater individual variability of MAD scores in SD. Although amphetamine did not alter MAD scores in any strain, methylphenidate selectively increased MAD scores in WKY and fluphenazine selectively increased MAD scores in SHR. WKY were also more sensitive than SHR and SD to the response-impairing effects of each drug. The finding that SHR showed a decrease in impulsivity following fluphenazine, but not following either amphetamine or methylphenidate, suggests that delay discounting in SHR may not represent a valid predictive model for screening effective ADHD medications in humans.

Keywords

attention-deficit/hyperactivity disorder; impulsivity; spontaneously hypertensive rat; amphetamine; methylphenidate; fluphenazine

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1. Introduction

Impulsive behavior is common among individuals diagnosed with attention-deficit/hyperactivity disorder (ADHD; Brennan and Arnsten, 2008). One manifestation of impulsivity, impulsive choice, reflects the preference for small, immediate rewards over larger rewards delivered after a delay (Perry and Carroll, 2008). Clinical laboratory studies have shown that both children (Schweitzer and Sulzer-Azaroff, 1995; Sonuga-Barke et al., 1992; Neef et al., 2005) and adults (Malloy-Diniz et al., 2007; Scheres et al., 2008) with ADHD make more impulsive choices than non-ADHD participants.

Stimulant medications, including amphetamine and methylphenidate, are a primary treatment option for ADHD (Kollins and March, 2007; Swanson and Volkow, 2009). Clinical studies have shown that these drugs are effective at reducing impulsivity in ADHD patients (Brown and Sleator, 1979; Malone and Swanson, 1993; Rapport et al., 1988; Solanto et al., 2001); in addition, methylphenidate also decreases impulsive choice in non-ADHD adult participants (Pietras et al., 2003). Preclinical studies have also shown that amphetamine (van Gaalen et al., 2006; Wade et al., 2000; Winstanley et al., 2005), atomoxetine (Navarra et al., 2008; Robinson et al., 2008), methamphetamine (Richards et al., 1999) and methylphenidate (Adriani et al., 2007; Pitts and McKinney, 2005; van Gaalen et al., 2006) reduce impulsive choice in rats, although amphetamine (Evenden and Ryan, 1996; Perry et al., 2008) and methylphenidate (Milstein et al., 2008; Navarra et al., 2008; Puumala et al., 1996; van den Bergh et al., 2006) either increased, or produced mixed effects, on impulsive choice in other rat studies. The discrepant findings in the preclinical literature illustrate the need for additional research focused on enhancing the predictive validity of animal models.

A variety of animal models have been used to investigate the neurobiology of impulsivity (Adriani et al., 2003; Davids et al., 2003). The spontaneously hypertensive rat (SHR) is currently the most widely studied animal model of ADHD (Russell, 2007; Pardey et al., 2009; Sagvolden et al., 2005). Compared to the progenitor Wistar-Kyoto (WKY) rat strain, SHR complete fewer response chains under a paced fixed-consecutive-number schedule of reinforcement (Evenden and Meyerson, 1999), make more open-arm entries in an elevated plus maze (Ueno et al., 2002), switch more quickly to choosing small immediate rewards over larger rewards as the delay to the larger reward increases (Fox et al., 2008; Pardey et al., 2009) and exhibit poorer performance on lever-holding and differential-reinforcement-of-low-rates (DRL) tasks (Sanabria and Killeen, 2008); however, discordant findings have also been reported (Bizot et al., 2007; van den Bergh et al., 2006). There is also evidence to suggest that WKY exhibit distinct behavioral and neurochemical characteristics reminiscent of anxiety and depression (De la Garza and Mahoney, 2004; Drolet et al., 2002; Malkesman and Weller, 2009) that may also play a role in results obtained with SHR and WKY, prompting suggestions that studies using SHR would benefit from the inclusion of an outbred comparator rat stock in addition to WKY (Heal et al., 2008; Pardey et al., 2009). Further, recent evidence has shown that significant behavioral differences can occur even among rats of the same inbred strain if the animals are obtained from different vendors (Sagvolden et al., 2009). Thus, considering the relatively small number of studies which compared directly SHR to outbred rat strains for their response to stimulant medications on impulsive choice (Bizot et al., 2007; van den Bergh et al., 2006), and given that there is a larger body of literature using standard outbred rats in such studies, further research is warranted.

The purpose of the present investigation was to compare the performance of SHR, WKY and outbred Sprague-Dawley (SD) rat strains on a self-adjusting impulsive choice task (Perry et al., 2005). Since it has been suggested that the apparent strain differences between

SHR and WKY are reduced or eliminated once differences in baseline response rates are considered (Alsop, 2007), it was of interest to compare strains on performance in a discrete-trials task that is independent of differences in response rates. Further, there is evidence that the dopamine D₂ receptor agonist quinpirole attenuates striatal dopamine release more effectively in SHR than WKY (Linthorst et al., 1990), indicative of different basal dopamine activity. To address this possibility, we examined the potential strain-dependent acute effects of amphetamine (0.1–1.0 mg/kg) and methylphenidate (1.0–10 mg/kg). The dopamine receptor antagonist fluphenazine (0.1–1.0 mg/kg) was also tested to compare dopamine receptor blockade with the indirect agonists. Although antipsychotics are not generally considered as ADHD treatment medications, the use of these drugs has been recommended in special cases of ADHD, such as when ADHD is comorbid with oppositional defiant disorder (Hazell, 2010). By comparing impulsive choice of SHR and WKY with outbred SD, as well as the effects of dopaminergic drugs, the findings of this study should have implications for the SHR model of ADHD, as well as adding to the preclinical literature on stimulant drugs and impulsivity.

2. Results

2.1 Acquisition and baseline performance

Task acquisition and baseline performance of each strain are illustrated in Figure 1. There was no significant main effect of strain on number of sessions to task acquisition (Fig. 1A) or number of sessions to stable baseline performance (Fig. 1B). However, planned *a priori* comparisons revealed that baseline MAD scores at stability were significantly lower ($p < 0.05$) in SHR than in WKY, but not SD (Fig. 1C). The within-strain distributions of individual data presented in Fig. 1C are illustrated in Fig. 1D; these data more completely illustrate that the variability of scores were lower in SHR than SD, with the variability of WKY intermediate between SHR and SD. The within-session MAD scores for each strain over the 5 sessions in which stability criteria were met are illustrated in Figure 2. There were no significant effects or interactions for the strain or time factors, indicating that task performance was stable within those sessions.

2.2 Effects of amphetamine

The strain-dependent acute effects of amphetamine (0.1–1.0 mg/kg) are illustrated in Figure 3. For MAD scores (Fig. 3A), ANOVA revealed a significant main effect of dose [$F(4,84) = 3.78$, $p < 0.01$]; however, the effect of dose within each strain did not reach significance. There was no significant effect of strain, although the strain $\times$ dose interaction approached significance ($p = .066$). For mean free-choice trial response latency (Fig. 3B), ANOVA revealed a significant main effect of dose [$F(4,84) = 2.41$, $p < 0.05$], and a significant strain $\times$ dose interaction [$F(8,84) = 2.02$, $p < 0.05$]. Although post hoc tests did not reveal significant dose effects within any strain, 1.0 mg/kg of amphetamine increased the latency in WKY compared to SHR; 0.56 mg/kg of amphetamine also increased latency in WKY, but this difference was not significant due to high variability. There were no significant main effects or interactions for total number of responses (Fig. 3C) or total number of trials (Fig. 3D) completed within the session.

2.3 Effects of methylphenidate

The strain-dependent acute effects of methylphenidate (1.0–10 mg/kg) are illustrated in Figure 4. For MAD scores (Fig. 4A), ANOVA revealed significant main effects of strain [$F(2,21) = 5.61$, $p < 0.05$] and dose [$F(4,84) = 5.48$, $p < 0.01$], as well as a significant strain $\times$ dose interaction [$F(8,84) = 3.91$, $p < 0.01$]. Post hoc tests indicated that the effect of dose attained significance in WKY only [$F(4,39) = 5.55$, $p < 0.001$]; in those rats, both 5.6 and 10 mg/kg of methylphenidate produced significant increases in MAD scores relative to saline.

Based on additional probes of the overall dose $\times$ strain interaction, it was revealed that WKY had higher MAD scores than SHR at 5.6 and 10 mg/kg of methylphenidate. For mean free-choice trial response latency (Fig. 4B), ANOVA revealed a significant main effect of strain [$F(2,21)=3.29$, $p<0.05$]. Post hoc comparisons indicated that 5.6 and 10 mg/kg of methylphenidate increased the mean latency in WKY compared to SHR (5.6 mg/kg) and SD (5.6 and 10 mg/kg). For total number of responses (Fig. 4C), ANOVA revealed a significant main effect of strain [$F(2,21)=3.78$, $p<0.05$]. Post hoc comparisons indicated that WKY had decreased responses compared to SHR at 1.0 and 3.0 mg/kg of methylphenidate, and that WKY had decreased responses compared to both SHR and SD at 5.6 mg/kg of methylphenidate. For total number of trials completed (Fig. 4D), ANOVA revealed a significant strain $\times$ dose interaction [$F(8,84)=3.27$, $p<0.01$]. Post hoc comparisons indicated that 5.6 and 10 mg/kg of methylphenidate decreased the total number of trials completed in WKY relative to saline, and that 5.6 mg/kg of methylphenidate decreased the total number of trials completed in WKY compared to SHR and SD.

2.4 Effects of fluphenazine

The strain-dependent acute effects of fluphenazine (0.1–1.0 mg/kg) are illustrated in Figure 5. For MAD scores (Fig. 5A), ANOVA revealed a significant strain $\times$ dose interaction [$F(3,63)=3.68$, $p<0.01$], although the main effects of strain and dose did not reach significance. In subsequent within-strain analyses, the main effect of dose attained significance in SHR only ($p<0.05$), with 1.0 mg/kg of fluphenazine producing a significant increase in MAD scores relative to saline. Also, it was revealed that SHR had lower MAD scores than both SD and WKY (SD and WKY did not differ) at 0.1 mg/kg of fluphenazine; no other significant between-strain effects were observed across doses of fluphenazine. For mean free-choice trial response latency (Fig. 5B), there were no significant main effects or interactions. For total number of responses (Fig. 5C), ANOVA revealed a significant main effect of strain [$F(2,21)=4.24$, $p<0.05$] and a significant dose $\times$ strain interaction [$F(6,63)=2.19$, $p<0.05$]. Post hoc comparisons indicated that WKY had decreased responses compared to SHR at 0.1 mg/kg of fluphenazine, whereas WKY had decreased responses compared to both SHR and SD at 1.0 mg/kg of fluphenazine. For total number of trials completed (Fig. 5D), ANOVA revealed significant main effects of strain [$F(2,21)=10.24$, $p<0.01$] and dose [$F(3,63)=8.97$, $p<0.001$], as well as a significant strain $\times$ dose interaction [$F(6,63)=7.52$, $p<0.001$]. Post hoc comparisons indicated that 1.0 mg/kg of fluphenazine decreased the total number of trials completed in WKY compared to saline, and compared to SHR and SD.

3. Discussion

The present study is the first direct comparison of impulsive choice in SHR, WKY and SD rats on a self-adjusting delay task that calculates a MAD score, or the “indifference point”, between choice of a small, immediate reward and a larger reward presented after varying delays. Since no differences among strains were noted on the task acquisition measures, it appears that differences in learning were not a factor. In contrast, however, SHR had the lowest overall MAD scores (i.e., highest choice impulsivity) at baseline and after saline administration when tested across each drug. While the baseline MAD scores between SHR and WKY attained significance, SD were not significantly different than SHR in this regard, likely due to the greater variance in score distribution in that outbred strain. Thus, these results support previous findings showing that SHR make more impulsive choices than WKY (e.g., Hand et al., 2009; Pardey et al., 2009; Sagvolden and Xu, 2008), as well as outbred Long Evans (Sanabria and Killeen, 2008) and Wistar (Bizot et al., 2007) outbred strains, but conflict with a previous study using SD (Clements and Wainwright, 2006). Administration of amphetamine did not produce dose-related effects on MAD scores in any

strain, although WKY showed the greatest sensitivity to the response-impairing effects of amphetamine, reflected by increased response latency and a slight decrease in the number of trials completed. Sagvolden and Xu (2008) reported that amphetamine decreased both hyperactivity and impulsivity in SHR, but not WKY, on a visual discrimination task. In that study, however, some evidence of rate-dependency with amphetamine was found, as low baseline response rates of WKY were increased, while the higher baseline response rates of SHR were decreased. While Evenden and Robbins (1983) found that the effects of amphetamine on choice and response rate are dissociable, doses of amphetamine (0.56 and 1.0 mg/kg) that reduced MAD scores in WKY in the present study also increased response latency and decreased the number of trials completed. Finally, Hand et al. (2009) found that relatively high doses of amphetamine (i.e., 1.0 – 5.6 mg/kg) also failed to reduce impulsive choice in SHR, although impulsive choice was increased by amphetamine in WKY. Thus, strain differences in baseline response rates and/or sensitivity to the impairing effects of amphetamine should be considered when examining heritable differences in impulsive choice with free operant or discrete trials procedures.

In contrast to amphetamine, methylphenidate increased MAD scores of WKY at the 5.6 and 10 mg/kg doses, although these doses also increased response latency and decreased the number of responses and completed trials in this strain. These results are consistent with previous findings showing that similar doses of methylphenidate (5 and 10 mg/kg) disrupt performance of WKY, but not SHR, on a visual stimulus detection task (Thanos et al., 2009). Since different tasks require varying amounts of behavioral output, it may be that tests like the current discrete-trials impulsive choice procedure, which does not require high levels of operant responding, are less sensitive to drug doses that disrupt behavior in a particular strain.

It was interesting to note that fluphenazine selectively increased MAD scores (i.e., reduced impulsivity) in SHR. This finding, which was obtained with 1.0 mg/kg of fluphenazine, is intriguing because there was no corresponding alteration in total number of responses observed. In contrast, MAD scores of WKY and SD were not affected by fluphenazine at any dose. While the present study did not investigate the basis for the strain-dependent effects of fluphenazine (0.1 mg/kg), it is possible that differences in dopamine D₂ receptor function may be involved. Accordingly, SHR have elevated D₂ receptor expression in mesocorticolimbic structures (Vaughan et al., 1999), and show greater sensitivity to quinpirole-induced inhibition of electrically-stimulated DA release in striatum, yet greater sulpiride-induced dopamine release in nucleus accumbens (Russell et al., 1995), relative to WKY; whether these neurochemical differences also apply to SD is currently unknown. It should be noted, however, that fluphenazine also increased response latency and decreased the total number of responses and completed trials in WKY, but not SHR or SD. Thus, WKY are more sensitive than both SHR and SD to the response-impairing effects of stimulant drugs, as well as a nonselective dopamine antagonist.

It is possible that the addition of visual cues may lead to a different pattern of results with amphetamine and/or methylphenidate. Previous research has shown that behavior in impulsive choice tasks is sensitive to manipulations of the discriminative stimuli signaling each response option. For instance, Cardinal et al. (2000) used an impulsive choice task in which a stimulus light was illuminated to signal the delayed reinforcement condition in one group of rats, whereas another group of rats remained in the dark condition throughout the task. Results indicated that exposure to the cued delay resulted not only in quicker task acquisition rates, but also increased preference for the larger, delayed reward in the presence of amphetamine. In contrast, amphetamine increased impulsive choice for rats in the no-cue condition (Cardinal et al., 2000). It would be of interest to determine if signaled delay might

differentially affect either baseline performance, or interact with drug effects in a strain-specific manner, in SHR, WKY and/or SD rats.

The results of the present study, along with several prior reports using SHR (e.g., Bizot et al., 2007; Hand et al., 2009; van den Bergh et al., 2006), are not entirely concordant with clinical findings showing stimulant-induced decreases in impulsive behavior in humans (Conners, 2002; Malone and Swanson, 1993). The reason(s) for this discrepancy are not readily apparent, but may be influenced by a variety of variables beyond the species examined. In rat studies, for example, Bizot et al. (2007) found that methylphenidate (3 and 5 mg/kg) did not alter impulsivity assessed with a T-maze task in SHR, WKY or Wistar outbred rats, while other studies have shown increases in impulsivity using the 5-choice serial reaction time task (Blondeau and Dellu-Hagedorn, 2007; Milstein et al., 2008; Navarra et al., 2008). In another study, Ferguson et al. (2007) failed to observe differences among SHR, WKY and SD in acquisition of a task that requires the withholding a lever press response (differential reinforcement of low rates, DRL); strain-dependent differences in task disruption also were not observed following either amphetamine or methylphenidate. Thus, the current finding that SHR showed a decrease in impulsivity only following fluphenazine, but not following either amphetamine or methylphenidate, suggests further that results obtained in SHR based on the delay discounting procedure used in this study may not represent a valid predictive model for screening effective ADHD medications in humans.

4. Materials and methods

4.1. Animals

A total of 24 ($n = 8$ per strain) 8–10 week-old (shipping weights ~250–275 g) male SHR, WKY and SD rats (Harlan Industries, Indianapolis, IN) were used. All rats were housed individually in standard plastic cages in a temperature- and humidity-controlled facility set to a 12:12 hr light/dark cycle (lights on at 0700 hr). Rats were handled and acclimated to the colony for 1 week prior to the beginning of the experiment, which was conducted during the light phase. Rats were fed after the completion of each daily session. The food allotment for each rat was dependent upon the total number of pellets consumed during each daily session; that is, rats earning 1–11 pellets received 15 g of food, rats earning 12–33 pellets received 14 g of food, rats earning 34–55 pellets received 13 g of food, etc.). Rats had *ad libitum* access to water while in the home cage. Experimental protocols were in accordance with the 1996 NIH *Guide for the Care and Use of Laboratory Animals* and were approved by the Institutional Animal Care and Use Committee at the University of Kentucky.

4.2. Apparatus

Experiments were conducted in 24 standard operant conditioning chambers (ENV-001; MED Associates, St. Albans, VT) that had alternating aluminum and Plexiglas walls with metal rod floors. Each chamber was located inside a sound-attenuating chamber (ENV-018M; MED Associates). A recessed food tray (5×4.2 cm) was located 2 cm above the floor in the center of one of the aluminum walls, and retractable response levers were located 6 cm above the floor on each side of the food tray. A white stimulus light (28 v; 3 cm diameter) was mounted 6 cm above each lever. Responses were recorded and programmed consequences were controlled by a personal computer equipped with Med-PC software (Med Associates, St. Albans, VT).

4.3. Procedure

Experimental sessions began at approximately 1600 hr and were conducted 7 days per week. Each session consisted of 15 4-trial blocks, and lasted until the completion of 60 trials or after 2 hr (whichever occurred first). Each 4-trial block consisted of 2 forced-choice trials,

followed by 2 free-choice trials. The start of each forced-choice trial was signaled by extending a single lever into the chamber and illuminating the stimulus light above it; the other lever and stimulus light were presented on the next forced-trial. Once a response was made, the stimulus light above the lever was immediately turned off and the appropriate number of pellets was dispensed immediately or after a delay; responses had no consequence until initiation of the next trial. The two forced-choice trials in each of the 15 blocks served to demonstrate the reinforcement magnitude and delay associated with each lever to guide subsequent choice behavior in the free-choice trials, and to associate turning off the cue light with a timeout period where no pellets were available (i.e., to establish the cue lights as discriminative stimuli signaling the availability of reinforcers during active response periods). Free-choice trials were signaled by illumination of the stimulus lights above both levers and extension of each lever. A single response on one lever yielded one grain-based 45 mg pellet (PJA1-0045, Research Diets Inc., New Brunswick, NJ) delivered immediately, and a response on the other lever yielded three pellets delivered after an adjusting delay. In contrast to the forced-choice trials, where only a single lever was present, levers were not immediately retracted after each response in free-choice trials; rather, the inter-trial interval was signaled by turning off the cue lights. Following delivery of the reinforcer after the last free-choice trial within each block, both levers were retracted to signal the end of each 4-trial block.

Following each lever press, an inter-trial interval (ITI) was imposed so that each trial would last 60 s. The initial delay to the delivery of the larger reinforcer was 6 s during daily acquisition sessions, and subsequently the delay changed each day depending on free-choice trial performance on the previous session. Across trial blocks with each session, a lever response resulting in immediate reinforcement resulted in a 1-s decrease in the delay, whereas a response on the delayed reinforcement lever resulted in a 1-s increase in the delay (however, the lower and upper limits on the delay were 0 and 45 s, respectively). The delay was adjusted only after the third and fourth trials in each block (i.e., the free-choice trials). During the delay, the stimulus lights above each lever were turned off to signal the timeout period. The final delay for each session was used as the initial delay at the start of the next session during the initial acquisition phase of the experiment. A mean adjusted delay (MAD) was calculated at the end of each session by averaging all adjusting delays on the free-choice trials, and this procedure was repeated until MAD stabilized (i.e., MAD scores within a 5-s range of variability for 5 consecutive sessions, with no increasing or decreasing trends). For each rat, the average MAD score from the first 5 sessions of stable performance was subsequently used as the initial delay for the remainder of the experiment. These values served as a quantitative measure of impulsive choice, with low and high MAD scores indicative of high and low levels, respectively, of impulsive choice.

The acute dose effects of amphetamine (0.1, 0.3, 0.56 and 1.0 mg/kg, i.p.), methylphenidate (1.0, 3.0, 5.6 and 10 mg/kg, i.p.) and fluphenazine (0.1, 0.3, and 1.0 mg/kg, s.c.) were determined once behavior stabilized. The doses and routes of administration were chosen based on the literature (fluphenazine; cf. Craft and Stratmann, 1996) or from our own experience with these drugs (i.e., amphetamine and methylphenidate; Perry et al., 2008, Wooters et al., 2008). The order of dose testing was based on a Latin Square, and rats completed testing of one drug before testing the next drug. Drugs were also tested in a counterbalanced order, such that a comparable number of rats received amphetamine, methylphenidate or fluphenazine first. A saline injection was also incorporated into each Latin Square. Data from each of the 3 saline tests were subsequently averaged to create a single saline control value for each rat if the values were within a 3-s range; otherwise, saline was retested at a later date if outlier values that fell outside that range were obtained. The pretreatment interval for amphetamine and methylphenidate was 15 min prior to the session, whereas fluphenazine was given 45 min prior to the session. Each drug test session

was interspersed by ≥ 2 baseline sessions (i.e., no injections) to ensure that behavior remained stable prior to each test session. A 5-day washout period was also incorporated between testing new drugs.

4.4. Drugs

Dextroamphetamine hemisulfate salt and fluphenazine dimaleate salt were obtained from Sigma-Aldrich (St. Louis, MO). Methylphenidate hydrochloride was obtained from Mallinckrodt (St. Louis, MO). All drugs were prepared in 0.9% NaCl (saline) and injected in a volume of 1 ml/kg of body weight. Doses represent the salt weights.

4.5. Statistical analysis

Dependent measures are presented as the mean ($\pm$ S.E.M.) value as a function of strain and/or dose. For the initial acquisition and baseline performance phase, three dependent measures, including (1) number of sessions to task acquisition (i.e., the number of sessions until a rat completed all 60 trials within 2 hr), (2) number of sessions to MAD stability (i.e., when MAD scores across 5 sessions fell within a 5 s range with no increasing or decreasing trends based on visual inspection of the data) and (3) MAD scores at stability, were analyzed with separate one-factor analysis of variance (ANOVA) with strain as the between-subjects factor. For analysis of drug effects, four dependent measures, including 1) MAD scores; 2) mean response latency on free choice trials; 3) total number of responses on free choice trials (including the reinforced and nonreinforced responses; and 4) total number of trials completed, were analyzed with separate mixed-factor ANOVA for repeated measures, with strain as the between-subjects factor and dose as the within-subjects factor. When ANOVA revealed significant main effects or interactions, post hoc comparisons (Tukey's and/or Dunnett's) were also conducted. Results were declared statistically significant when $p \leq 0.05$.

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Fig. 1.

Acquisition and baseline performance of spontaneously hypertensive (SHR; white bars/circles), Wistar-Kyoto (WKY; black bars/circles) and Sprague-Dawley (SD; gray bars/circles) rats ($n=8$ per strain) on the delay discounting task. Bars represent the mean ($\pm$ S.E.M.) number of sessions to task acquisition (Panel A), the mean ($\pm$ S.E.M.) number of sessions to meet task stability criteria (Panel B) and the average mean adjusted delay (MAD) scores across the initial 5 sessions of stable performance (Panel C). Circles represent the individual distribution of MAD scores across the initial 5 sessions of stable performance within each strain (Panel D). Asterisk indicates a significant difference using *a priori* t test ($*p<0.05$).

Fig. 2. Within-session MAD scores collapsed across the initial 5 sessions of stable performance of spontaneously hypertensive (SHR; white circles), Wistar-Kyoto (WKY; black circles) and Sprague-Dawley (SD; gray circles) rats ($n=8$ per strain) on the delay discounting task. Data points represent the mean ($\pm$ SEM) mean adjusted delay (MAD) in sec. No significant effects were obtained among strains at any time interval.

Fig. 3. Acute effects of amphetamine (0.1–1.0 mg/kg, i.p.) in spontaneously hypertensive (SHR; white circles), Wistar-Kyoto (WKY; black circles) and Sprague-Dawley (SD; gray circles) rats ($n=8$ per strain) on the delay discounting task. Data points represent the mean ($\pm$ SEM) of the following: (Panel **A**) mean adjusted delay (MAD) in sec; (Panel **B**) mean free-choice trial response latency; (Panel **C**) total free-choice trial responses; and (Panel **D**) total number of completed trials. Letter represents a significant difference compared to SHR at the same dose (a , $p<0.05$).

Fig. 4.

Acute effects of methylphenidate (1.0–10 mg/kg, i.p.) in spontaneously hypertensive (SHR; white circles), Wistar-Kyoto (WKY; black circles) and Sprague-Dawley (SD; gray circles) rats ($n=8$ per strain) on the delay discounting task. Data points represent the mean ($\pm$ SEM) of the following: (Panel **A**) mean adjusted delay (MAD) in sec; (Panel **B**) mean free-choice trial response latency; (Panel **C**) total free-choice trial responses; and (Panel **D**) total number of completed trials. Asterisk represents a significant within-strain difference compared to saline (S) injection (*, $p<0.05$). Letters represent a significant difference compared to SHR (*a*, $p<0.05$) or SD (*b*, $p<0.05$) at the same dose. Hash sign represents a significant difference compared to both of the other strains at same dose (#, $p<0.05$).

Fig. 5.

Acute effects of fluphenazine (0.1–1.0 mg/kg, s.c.) in spontaneously hypertensive (SHR; white circles), Wistar-Kyoto (WKY; black circles) and Sprague-Dawley (SD; gray circles) rats ($n=8$ per strain) on the delay discounting task. Data points represent the mean ($\pm$ SEM) of the following: (Panel A) mean adjusted delay (MAD) in sec; (Panel B) mean free-choice trial response latency; (Panel C) total free-choice trial responses; and (Panel D) total number of completed trials. Asterisk represents a significant within-strain difference compared to saline (S) injection (*, $p<0.05$). Letter represents a significant difference compared to SHR at the same dose (a , $p<0.05$). Hash sign represents a significant difference compared to both of the other strains at the same dose (#, $p<0.05$).