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Effects of dopamine agents on a schedule-induced polydipsia procedure in the spontaneously hypertensive rat and in Wistar control rats

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Abstract

The spontaneously hypertensive rat (SHR) has been proposed as an animal model for attention deficit hyperactivity disorder (ADHD), and typically develops excessive patterns of response under most behavioural protocols. Schedule-induced polydipsia (SIP) is the excessive water consumption that occurs as a schedule effect when food is intermittently delivered and animals are partially food- but not water-deprived. SIP has been used as a model of excessive behaviour, and considerable evidence has involved the dopaminergic system in its development and maintenance. The aim of this study was to evaluate the effects of the most common psychostimulants used in ADHD treatment on SIP, comparing their effects in SHRs with rats from control populations. SHR, Wistar Kyoto (WKY) and Wistar rats were submitted to a multiple fixed time (FT) food schedule with two components: 30s and 90s. The acute effects of different dopaminergic compounds were evaluated after 40 sessions of SIP acquisition. All animals showed higher adjunctive drinking under FT 30 s than FT 90s, and SHRs displayed higher asymptotic SIP levels in FT 90 s compared to WKY and Wistar rats. SHRs were less sensitive to dopaminergic agents than control rats in terms of affecting rates of adjunctive drinking. These differences point to an altered dopaminergic system in the SHR and provide new insights into the neurobiological basis of ADHD pharmacological treatments.

Keywords

Schedule-induced polydipsia, d-amphetamine, methylphenidate, dopamine, SHR, WKY, Wistar rats

Introduction

Intermittent delivery of food is the basis for the development of behavioural expressions over the course of successive inter-food intervals. Schedule-induced polydipsia (SIP) occurs if water is available throughout these intervals, provided that animals are partially food-deprived (Falk, 1961). Once SIP has developed, animals regularly lick/drink after the delivery of each food pellet. There has been a considerable debate on the possible behavioural mechanisms that might be involved in SIP and other related behaviours (see Killeen and Pellón, 2013).

SIP can be observed both in interval- and time-food schedules, and depends on food-related variables such as food deprivation, food frequency and food magnitude (Castilla and Pellón, 2013, Falk, 1966, 1967; Flory, 1971). The procedure has been proposed as a model of behavioural excess (Lau et al., 1996), and thus can be related to disorders that concur with forms of excessiveness, such as compulsive behaviours (Moreno and Flores 2012; Platt et al., 2008), drinking in schizophrenia (Hawken and Beninger, 2013) or addictions (e.g. drug addiction: Gilpin et al., 2008).

The spontaneously hypertensive rat (SHR) easily acquires and maintains SIP, even under time schedules in which control rats barely develop it (Íbias and Pellón, 2011, 2014). The SHR has the main characteristics that define attention deficit hyperactivity disorder (ADHD): impulsivity (Evenden and Meyerson, 1999), inattention (Berger and Sagvolden, 1998) and hyperactivity (Sagvolden, 2000). Accordingly, SHR has generally been validated

as the best model for studying ADHD (e.g. Adriani et al., 2003; Langen and Dost 2011; Meneses et al., 2011; Roessner et al. 2010), with evidence in favour of representing the hyperactive subtype of the disorder (Sagvolden et al., 2009; Sutherland et al., 2009), despite a good number of reports that question its validity in regard to some aspects of ADHD (e.g. Alsop, 2007; Sanabria and Killeen, 2008).

Several theories point to the dynamics of the dopaminergic system as a key component of ADHD. It has been proposed that a dysfunction in the dopamine (DA) mesolimbocortical pathway produces both altered reinforcement and extinction processes in individuals diagnosed with this disorder (Johansen et al., 2002). The DA hypothesis has received support based on the alleviation of ADHD symptoms by means of psychostimulant drugs which act at the dopaminergic synapses, such as methylphenidate (MPH), d-amphetamine (d-AMP) and pemoline (Baroni and Castellanos,

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2015; Findling, 2008; Safer and Krager, 1988; Seiden et al., 1993). In this sense, an altered dopaminergic function in the SHR strengthens the validity of this rat as a model of ADHD (Heijtz et al., 2007; Langen and Dost, 2011; Russell, 2003).

Studies evaluating the implication of the dopaminergic system in SIP through the use of pharmacological compounds that modify DA actions have generally shown a reduction in behaviour (Didriksen and Christensen, 1993; Didriksen et al., 1993; Flores and Pellón, 1997; Kaempf and Porter, 1987; Pellón and Blackman, 1992; Piazza et al., 1993; Snodgrass and Allen, 1987). Mittleman et al. (1994) concluded that the dopaminergic neurotransmission is involved in the motor, but not in the motivational, component of SIP; however, Pellón et al. (2011) suggested that DA D₂ receptors are related to the motor aspects of SIP, whereas DA D₁ receptors are more involved in the motivational components, not ruling out possible interactions between them.

The present study evaluates the effects of d-AMP and MPH on SIP performance of SHR and control rats in two fixed time (FT) schedules, with short versus long inter-food intervals that, respectively, lead to high or low levels of drinking. The effects of selective agonists and antagonists of both DA D₁ and D₂ receptors were also evaluated. Different effects were expected in SHRs as compared to control rats given their differential dopaminergic activity, particularly in terms of the resistance to reduction by psychostimulants due to their demonstrated persistence in behaviour (e.g., Íbias and Pellón, 2011; Íbias et al., 2015).

Materials and methods

Subjects

We used 24 male rats belonging to three different strains – eight SHR, eight WKY and eight Wistar rats – obtained from Charles Rivers Laboratories (Lyon, France). On arrival, rats were ten weeks old. They were initially housed in groups of four, and once habituated to the animal facility (after ten days), they were housed singly in 18 cm×32 cm×20.5 cm transparent plexiglass cages with a metal grid as a detachable roof to allow food to be deposited and a water bottle to be fitted. The room environment was continuously controlled with a 12-h light–dark cycle (light from 08:00 to 20:00 hours), ambient temperature of 17–23 °C, and 60% relative humidity.

At the start of the experiment, animals were in their 12th week of life, and they had the following mean (\pm SEM) weights: SHR 291.98 \pm 2.78 g (range: 277–302 g); WKY 338.88 \pm 5.78 g (range: 306–361 g); Wistar 372.50 \pm 2.59 g (range: 359–384 g). Animals' weights were gradually reduced by controlled feeding to 80%–85% of their free-feeding body weights with reference to a standard growth curve for each strain. This criterion was maintained throughout the entire procedure. Rats were weighed before each experimental session, and a supplement of food was given at least 20 min after the end of every session to maintain their weights under criterion. Water was freely available to all animals in their home cages. All animal care procedures were in accordance with the European Union Council Directive 2010/63 and the Spanish Royal Decree 53/2013 for minimizing stress and discomfort in animals.

Apparatus

We used eight Leticia LI-836 conditioning chambers, which have been described extensively before (e.g. Íbias et al., 2015). A bottle of water was fitted to the external right-hand side of each box,

and rats had access to the spout from the interior of the chamber. The contact between the animal's tongue and the metal spout completed the electric circuit between the 12-bar metal grid, which served as the floor, and the water-bottle spout. 45-mg food pellets (Bio-Serv, Frenchtown, NJ, USA) were dispensed in an aperture of the chamber's front wall, situated 3.7 cm from the floor, where magazine entries were recorded by a photo-beam system. Licks and magazine entries were recorded using a MED-PC-IV application under a Windows XP environment. The chambers were lit by an indirect 25 W light fitted to the interior of the soundproof housing that insulated each chamber, and two 3 W lamps situated on the front panel on either side of the food hopper. Within each chamber, a fan producing background noise of approximately 60 dB masked any exterior noise. At the top of the front wall of each chamber was a speaker to produce sound signals when necessary.

Procedure

SIP acquisition and maintenance. In order to stabilize baseline rates of behaviour, a SIP procedure was carried out daily for 40 consecutive sessions. A multiple FT schedule was used, in which a food pellet was delivered at regular intervals regardless of the animal's behaviour. Each experimental session contained two separate components of FT 30 s and FT 90 s, where 20 food pellets were delivered in each component. To facilitate the discrimination of the current FT, one of these components was signalled with a continuous 60 dB tone, which was randomized between animals for a given FT. The illumination of the experimental chambers was totally turned off for 60 s between both FT schedules, and the FT component that initiated each session was randomized between and within animals. The choice of using a multiple instead of a simple food schedule was to control for individual differences within a given strain of rats, and also to reduce to a minimum the number of animals used. Previous studies from our laboratory have employed with success multiple food schedules for pharmacological testing (e.g. Flores and Pellón, 1995; Pérez-Padilla and Pellón, 2007).

The rate of licks and magazine entries from the last five sessions were analysed in order to compare steady-state levels of responding during each FT schedule. Water consumption was also recorded. Only overall water consumption at the beginning and end of the behavioural training will be reported in order to characterize excessive drinking. No other measure of water consumption was analysed, as the intake could not be differentiated among FT schedules since animals drank from the same bottle in the two components.

Pharmacological procedure. After completion of the aforementioned 40 sessions, different drug doses were tested on licks and magazine entries to determine dose–response curves. The procedure was carried out across a series of five experimental sessions per week (Mondays to Fridays), followed by two rest days. To prevent any carry-over effect of the different drug doses, only two drug doses per week were administered, on Tuesdays and Fridays. Mondays and Wednesdays were behavioural control sessions without any treatment (only data from Mondays were considered for analyses). Vehicle (saline solution, 0.9% sodium chloride) control sessions were carried out on Thursdays.

The following drugs and doses were administered: d-AMP (0.1, 0.3, 1.0 and 1.5 mg/kg), MPH (0.6, 2.5, 5.0 and 10.0 mg/kg),

Table 1. Drug-administration schedule. The table depicts the pharmacological procedure followed to administer the different drugs and their doses, as well as the weekly schedule for drug administration. The first drug administered was d-amphetamine, and the order of the doses was randomized for each drug, avoiding more than one dose in the 'high range' per week.

Order of drug administration and dosages							
Order	Drug	Doses (mg/kg)				Order of the doses (mg/kg)	
1	d-amphetamine	0.1	0.3	1.0	1.5	(0.3, 1.0, 0.1, 1.5)	
2	Eticlopride	0.001	0.003	0.01	0.1	(0.1, 0.01, 0.003, 0.001)	
3	SCH 23390	0.001	0.003	0.01		(0.001, 0.003, 0.01)	
4	SKF 38393	1.0	3.0	5.6		(1.0, 5.6, 3.0)	
5	Quinpirole	0.003	0.01	0.03	0.1	(0.003, 0.03, 0.01, 0.1)	
6	Methylphenidate	0.6	2.5	5.0	10.0	(10.0, 0.6, 5.0, 2.5)	

Weekly schedule for drug administration							
DAY	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Session	Behaviour	Drug	Behaviour ^a	Vehicle	Drug	Rest	Rest

^aOnly data from Mondays were considered for analyses.

the DA D₁ receptor agonist SKF 38393 (1.0, 3.0 and 5.6 mg/kg), the DA D₂ receptor agonist quinpirole (0.003, 0.01, 0.03 and 0.1 mg/kg), the DA D₁ receptor antagonist SCH 23390 (0.001, 0.003 and 0.01 mg/kg) and the DA D₂ receptor antagonist eticlopride (0.001, 0.003, 0.01 and 0.1 mg/kg). All drug doses were dissolved in 0.9% saline and administered intraperitoneally in a volume of 1 ml/kg (except 10.0 mg/kg MPH at a volume of 2.5 ml/kg). Furthermore, d-AMP was administered 10 min before the start of the session, MPH and SCH 23390 15 min before and SKF 38393, Quinpirole and Eticlopride 30 min prior to session commencement. Drug doses and time intervals between injections were selected following the protocols of Pellón et al. (2007) and Askenasy et al. (2007). The procedure lasted 12 weeks, the sequence in which the drugs were tested was as described above and the order of doses for a given drug was determined at random. Each dose was tested once, and all animals received the same dose in the same day. Table 1 summarizes the pharmacological procedure. Average rates per session were taken both for licks and magazine entries to obtain dose–response curves for each drug.

Statistical analyses

To compare baseline behaviour after SIP acquisition, we used ANOVA tests with a 'strain' factor with three levels (SHR, Wistar and WKY) and the average of the last five sessions on licks/min, magazine entries/min and volume of water consumed. We also used repeated measures ANOVA tests to evaluate possible effects of the order of presentation of the FT schedules. We used the 'strain' factor (three levels), a 'session' factor with five levels (one per session), and a 'FT' factor with two levels (FT 30 s and FT 90 s).

Before evaluating the effect of any drug, the results of every vehicle session and its respective behavioural control session was compared using ANOVA tests that were performed to rule out any possible altering effect of the injection or the weekend interruption. Therefore, we used the 'strain' factor and a repeated measure factor, 'injection', with two levels (behavioural control and vehicle). To analyse the effects of each drug on licks/min and magazine entries/min, we used ANOVA tests, each analysis including the 'strain' factor and a repeated measure factor, 'dose',

corresponding to the doses of the specific drugs (being vehicle considered as the 0 mg/kg dose). Post-hoc comparisons were carried out using pairwise comparisons with a Bonferroni's adjustment, and the minimum criteria of significance was set at $\alpha=0.05$. Statistical analyses were carried out using SPSS® 19.

Results

Acquisition of licks and magazine entries

After 40 experimental sessions, animals reached steady-state levels of schedule-induced licking in both FT schedules (see Íbias et al., 2015 for a detailed report of these acquisition data). Reaching stable behaviour was critical before starting the pharmacological procedure, as it was necessary that any possible alteration in response rates after drugs' treatment was limited to the drug sessions. The last five sessions were selected as representative of final response rates.

The order of the FT schedule presentation (FT 30 s vs FT 90 s) did not affect the rates of behaviour through the last five sessions of acquisition for a given FT, as no significant 'session×FT' interaction was found either for licks ($F(2,21)=0.15$, $p<0.43$) or magazine entries ($F(2,21)=2.50$, $p<0.11$). Therefore, animals showed stable levels of behaviour from one session to the next, regardless of which FT commenced the session. In addition, water consumption did not change among these last five sessions, since no significant 'session' effect was found ($F(4,18)=2.16$, $p<0.12$).

Results also showed no differences in the last five sessions of acquisition between strains in FT 30 s (mean±SEM of licks/min for SHR, WKY and Wistar rats were, respectively, 56.81±6.65, 43.91±9.65 and 40.16±9.16, and mean±SEM of entries/min 31.54±5.40, 29.53±2.26 and 28.16±3.64, respectively). However, in FT 90 s, a 'strain' effect ($F(2,21)=13.35$, $p<0.01$) was found, as SHRs showed higher licks/min than WKY and Wistar rats ($p<0.01$ for both comparisons), with means±SEM of 24.81±2.74, 7.70±2.16 and 9.11±2.84 for SHR, WKY and Wistar rats, respectively. No differences were found in FT 90 s when comparing the different strains of rats in magazine entries/min (being the means±SEM for SHR,

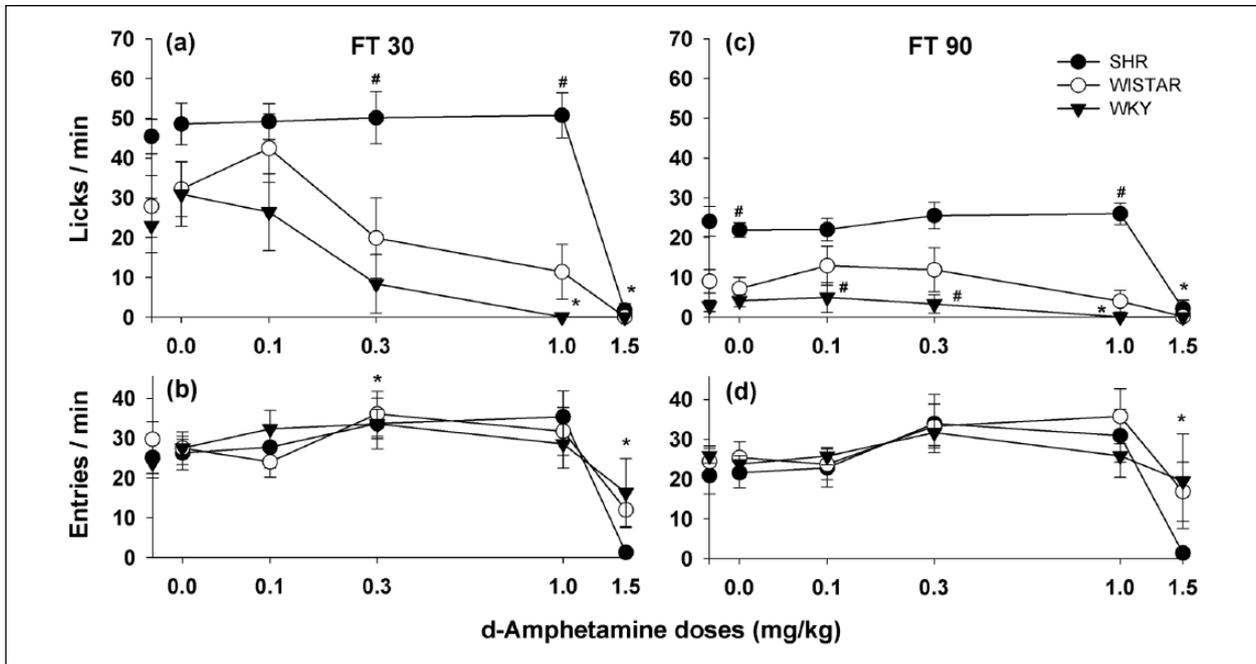


Figure 1. Dose-response functions for d-AMP in terms of mean (\pm SEM) licks per minute (upper panels) and mean (\pm SEM) magazine entries per minute (bottom panels) for SHR, Wistar and WKY rats during the FT 30 s (left panels) and FT 90 s (right panels) schedules. Data from the behavioural control sessions are shown over the y axis, and the doses are represented in logarithmic scale. (a) $\#p < 0.05$ for SHR vs Wistar or WKY. $*p < 0.05$ dose comparisons vs vehicle for Wistar and WKY, and 1.5 mg/kg vs all other doses for SHR. (b) $*p < 0.05$ dose comparisons vs vehicle at 0.3 mg/kg, and vs all other doses at 1.5 mg/kg. (c) $\#p < 0.05$ for SHR vs WKY, and also vs Wistar at vehicle and 1.0 mg/kg. $*p < 0.05$ dose comparisons vs vehicle for all groups. (d) $*p < 0.05$ dose comparisons vs all other doses. ($N=24$.)

WKY and Wistar rats 25.52 ± 4.38 , 31.39 ± 2.46 and 25.78 ± 3.82 , respectively). Magazine entries neither differed from those observed in FT 30 s nor changed despite differences in licking behaviour related to the SIP procedure. With regard to the volume of water consumed, mean \pm SEM mL throughout the last five sessions were 13.20 ± 0.64 for SHR, 8.85 ± 0.99 for Wistar and 7.78 ± 1.31 for WKY, which represents an increase over the initial consumption of 4.18 ± 0.67 for SHR, 2.38 ± 0.49 for Wistar and 2.55 ± 0.35 for WKY found during the first five sessions. Water consumption tripled across acquisition sessions, and can be considered to have reached thresholds above simple prandial drinking, thus reflecting SIP. SHR licked at a higher rate than the other rats during FT 90 s, and, hence, drank more water than both Wistar and WKY ($F(2,21)=9.24$, $p < 0.01$), yet no significant differences were found between strains in lick efficiency (licks per mL of water) ($F(2,21)=1.79$, $p > 0.50$). Mean \pm SEM estimations of lick efficiency were: 97.76 ± 9.79 for SHR, 68.51 ± 11.77 for Wistar and 78.16 ± 14.81 for WKY.

Drug effects on rates of licks and magazine entries

Neither the licks analysis nor the magazine-entries analysis revealed effects for ‘injection’ or ‘strain \times injection’ interaction with any drug or FT schedule, when the data of vehicle and behaviour control sessions were compared.

d-AMP. Analysis of licks/min in FT 30 s (Figure 1(a)) revealed a ‘strain \times dose’ interaction ($F(8,84)=5.55$, $p < 0.01$): SHR showed

higher rates of licks compared to WKY and Wistar rats, especially under the doses of 0.3 and 1.0 mg/kg ($p < 0.01$). WKY and Wistar showed a gradual dose-dependent decrease with differences when comparing the highest dose of 1.5 mg/kg with vehicle ($p < 0.01$ for both comparisons). In SHRs, licks/min decreased at the highest dose with respect to all other doses including vehicle ($p < 0.01$). Analysis of magazine entries (Figure 1(b)) showed a ‘dose’ effect ($F(4,84)=2.04$, $p < 0.05$), with an increase at the dose of 0.3 mg/kg compared to vehicle ($p < 0.02$) and a decrease at the dose of 1.5 mg/kg respect to all other doses ($p < 0.01$ for all comparisons).

Analysis of licks/min in FT 90 s (Figure 1(c)) showed a ‘strain \times dose’ interaction ($F(8,84)=4.69$, $p < 0.01$): SHR showed higher rates of licks compared to Wistar and WKY at vehicle and 0.1 mg/kg ($p < 0.01$ for all comparisons), and at 0.3 mg/kg compared to WKY ($p < 0.01$). Analysis of magazine entries (Figure 1(d)) showed a ‘dose’ effect ($F(4,84)=11.69$, $p < 0.01$), with a decrease at the dose of 1.5 mg/kg with respect to all other doses ($p < 0.01$ for all comparisons).

Regardless of the FT schedule, d-AMP was less efficacious in reducing licks in SHR in comparison to Wistar and WKY controls. Rate of magazine entries remained fairly constant across d-AMP doses, except at the highest dose of 1.5 mg/kg, which abruptly reduced entries, particularly in SHR.

MPH. Analysis of licks/min in FT 30 s (Figure 2(a)) showed a ‘dose’ effect ($F(4,84)=21.57$, $p < 0.01$), where doses higher than 0.6 mg/kg resulted in a decrease in licks ($p < 0.01$). Analysis of magazine entries (Figure 2(b)) showed a ‘strain \times dose’ interaction

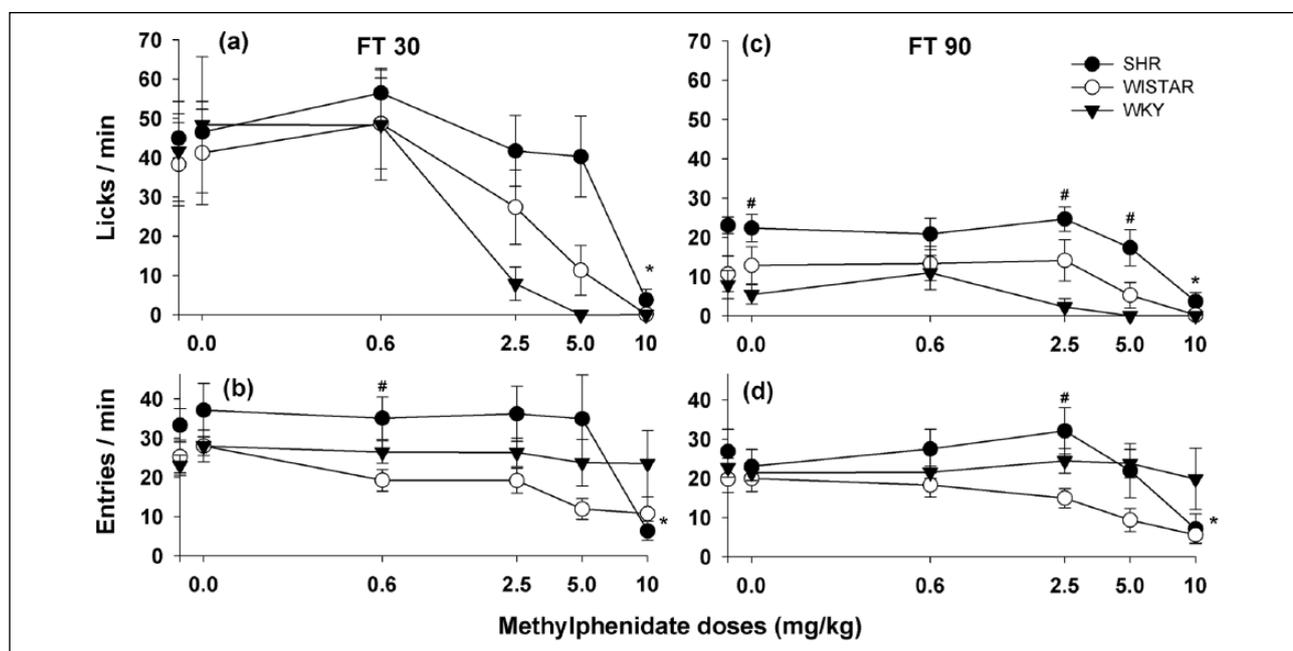


Figure 2. Dose–response functions for MPH in terms of mean (\pm SEM) licks per minute (upper panels) and mean (\pm SEM) magazine entries per minute (bottom panels) for SHR, Wistar and WKY rats during the FT 30 s (left panels) and FT 90 s (right panels) schedules. Data from the behavioural control sessions are shown over the y axis, and the doses are represented in logarithmic scale. (a) $*=p<0.05$ dose comparisons vs vehicle. (b) $\# = p<0.05$ for SHR vs Wistar. $*=p<0.05$ dose comparisons vs all other doses for SHR. (c) $\# = p<0.05$ for SHR vs WKY, and also vs Wistar at 5.0 mg/kg. $*=p<0.05$ dose comparisons vs all other doses for all groups. (d) $\# = p<0.05$ for SHR vs Wistar. $*=p<0.05$ dose comparisons vs all other doses for SHR. ($N=24$.)

($F(8,84)=2.04$, $p<0.05$): SHR performed more entries at the 0.6 mg/kg dose compared to Wistar ($p<0.05$), and performed fewer entries at the highest dose of 10 mg/kg compared to all other doses ($p<0.01$ for all comparisons).

Analysis of licks/min in FT 90 s (Figure 2(c)) showed a ‘strain \times dose’ interaction ($F(8,84)=2.11$, $p<0.05$) that revealed differences between SHR and WKY at vehicle and 2.5 mg/kg ($p<0.01$), and SHR in comparison to Wistar and WKY at 5 mg/kg ($p<0.05$ and $p<0.01$, respectively). The highest dose of 10 mg/kg resulted in a decrease in licks in all groups ($p<0.05$ for all comparisons). Analysis of magazine entries (Figure 2(d)) revealed a ‘strain \times dose’ interaction ($F(8,84)=2.25$, $p<0.05$): SHRs performed more entries at 2.5 mg/kg compared to Wistar ($p<0.05$), and performed fewer entries at the highest dose of 10 mg/kg compared to all other doses ($p<0.01$ for all comparisons).

Regardless of the FT schedule, MPH was less efficacious in reducing licks in SHR when compared to Wistar and WKY rats. Magazine entries rate abruptly decreased in SHR at the 10.0 mg/kg dose of MPH, both in FT 30 s and FT 90 s schedules.

SKF 38393. Analysis of licks in FT 30 s (Figure 3(a)) revealed no ‘strain’, ‘dose’ or interaction effects; and the analysis of magazine entries (Figure 3(b)) only showed a ‘dose’ effect ($F(3,63)=3.89$, $p<0.01$).

Analysis of licks in FT 90 s (Figure 3(c)) revealed a ‘strain’ effect ($F(2,21)=23.09$, $p<0.01$), with higher rates of licks in SHR. Analysis of magazine entries (Figure 3(d)) revealed only a ‘dose’ effect ($F(3,63)=28.43$, $p<0.01$), with a decrease in entries at the 5.6 mg/kg dose with respect to vehicle ($p<0.01$).

There were no ‘strain’ differences related to the effect of SKF 38393 either in licks or in magazine entries.

Quinpirole. Analysis of licks in FT 30 s (Figure 4(a)) revealed a ‘strain’ effect ($F(2,21)=10.30$, $p<0.01$), with SHR performing more licks than both Wistar and WKY ($p<0.01$ in both cases). A ‘dose’ effect ($F(4,84)=28.31$, $p<0.01$) reflected a gradual dose-dependent decrease in licks at doses above 0.01 mg/kg ($p<0.01$ for all comparisons). Analysis of magazine entries (Figure 4(b)) revealed a ‘strain \times dose’ interaction ($F(8,84)=2.50$, $p<0.05$): WKY performed fewer entries at 0.1 mg/kg compared to SHR, and compared to vehicle ($p<0.05$ for both comparisons).

Analysis of licks in FT 90 s (Figure 4(c)) revealed a ‘strain \times dose’ interaction ($F(8,84)=5.42$, $p<0.01$): SHRs performed more licks compared to Wistar and WKY rats at all the doses tested except 0.1 mg/kg, as well as under vehicle ($p<0.01$ in all cases). Analysis of magazine entries (Figure 4(d)) also revealed a ‘strain \times dose’ interaction ($F(8,84)=7.61$, $p<0.01$): SHRs performed more entries at 0.1 mg/kg compared to Wistar and WKY rats ($p<0.01$ for both comparisons).

Quinpirole dose-dependently reduced licking rates in all strains at both FT schedules, but showed a tendency to be less efficacious in SHR when compared to Wistar and WKY controls. The highest dose of quinpirole reduced magazine entries in WKY during FT 30 s and FT 90 s schedules (also a bit in Wistar at FT 90 s), but animals were barely licking at this dose of quinpirole, even SHR rats.

SCH 23390. Analysis of licks in FT 30 s (Figure 5(a)) revealed no ‘strain’ effect, but a ‘dose’ effect ($F(3,63)=45.31$, $p<0.01$),

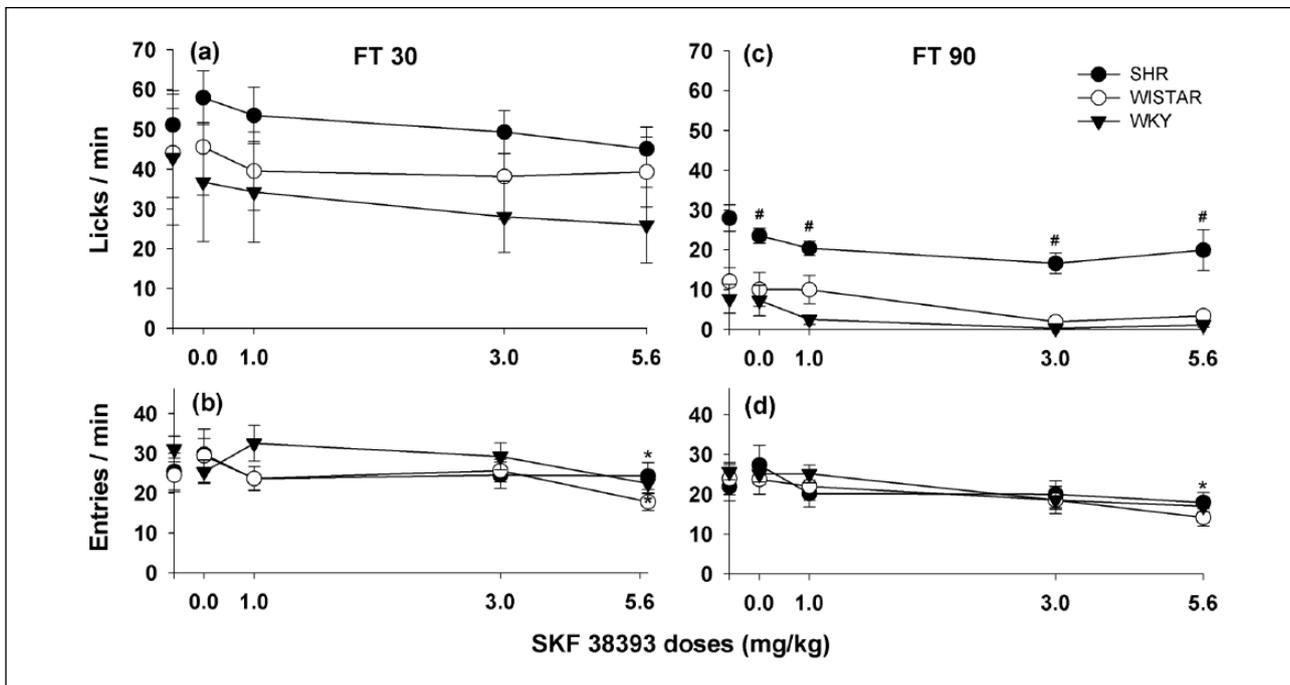


Figure 3. Dose–response functions for SKF 38393 in terms of mean (\pm SEM) licks per minute (upper panels) and mean (\pm SEM) magazine entries per minute (bottom panels) for SHR, Wistar and WKY rats during the FT 30 s (left panels) and FT 90 s (right panels) schedules. Data from the behavioural control sessions are shown over the y axis, and the doses are represented in logarithmic scale. (b) $*=p<0.05$ for 1.0 mg/kg vs 5.6 mg/kg. (c) $\#=p<0.05$ for SHR vs Wistar or WKY. (d) $*=p<0.05$ dose comparisons vs vehicle. ($N=24$.)

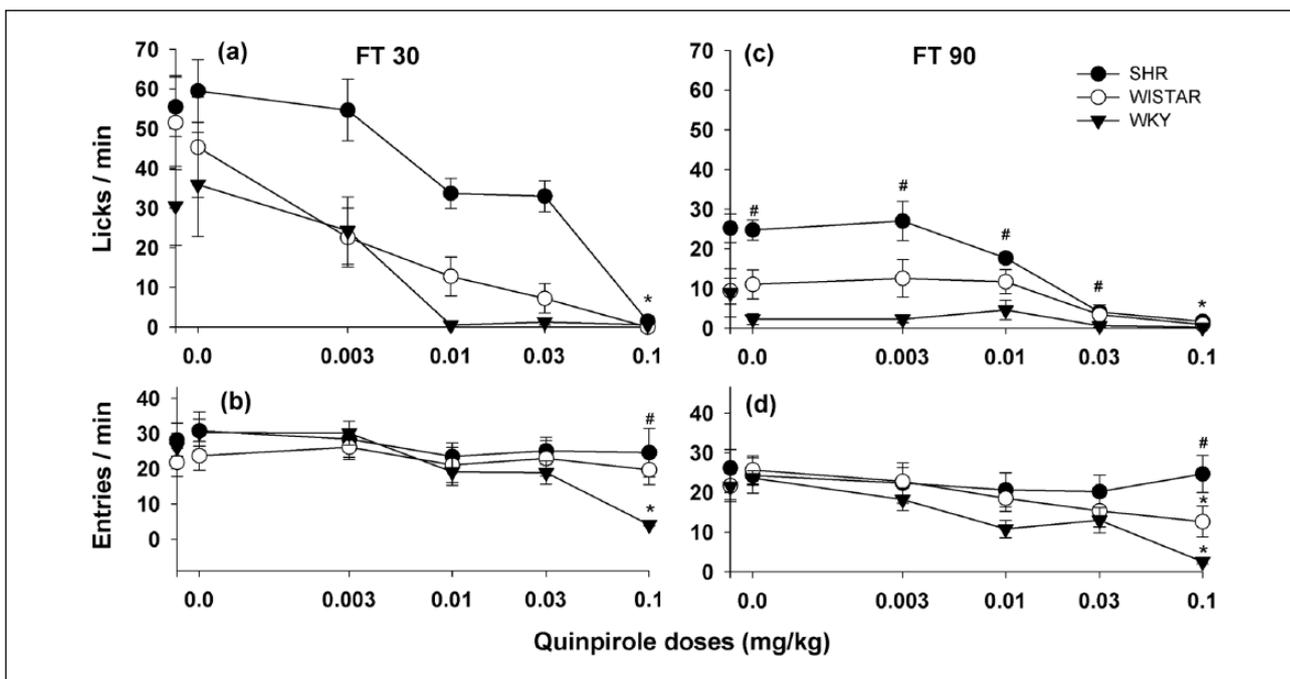


Figure 4. Dose–response functions for quinpirole in terms of mean (\pm SEM) licks per minute (upper panels) and mean (\pm SEM) magazine entries per minute (bottom panels) for SHR, Wistar and WKY rats during the FT 30 s (left panels) and FT 90 s (right panels) schedules. Data from the behavioural control sessions are shown over the y axis, and the doses are represented in logarithmic scale. (a) $*=p<0.05$ dose comparisons vs vehicle. (b) $\#=p<0.05$ for SHR vs WKY. $*=p<0.05$ dose comparison vs vehicle for WKY. (c) $\#=p<0.05$ for SHR vs Wistar or WKY. $*=p<0.05$ dose comparison vs vehicle for SHR. (d) $\#=p<0.05$ for SHR vs Wistar or WKY. $*=p<0.05$ dose comparisons vs vehicle for Wistar and WKY. ($N=24$.)

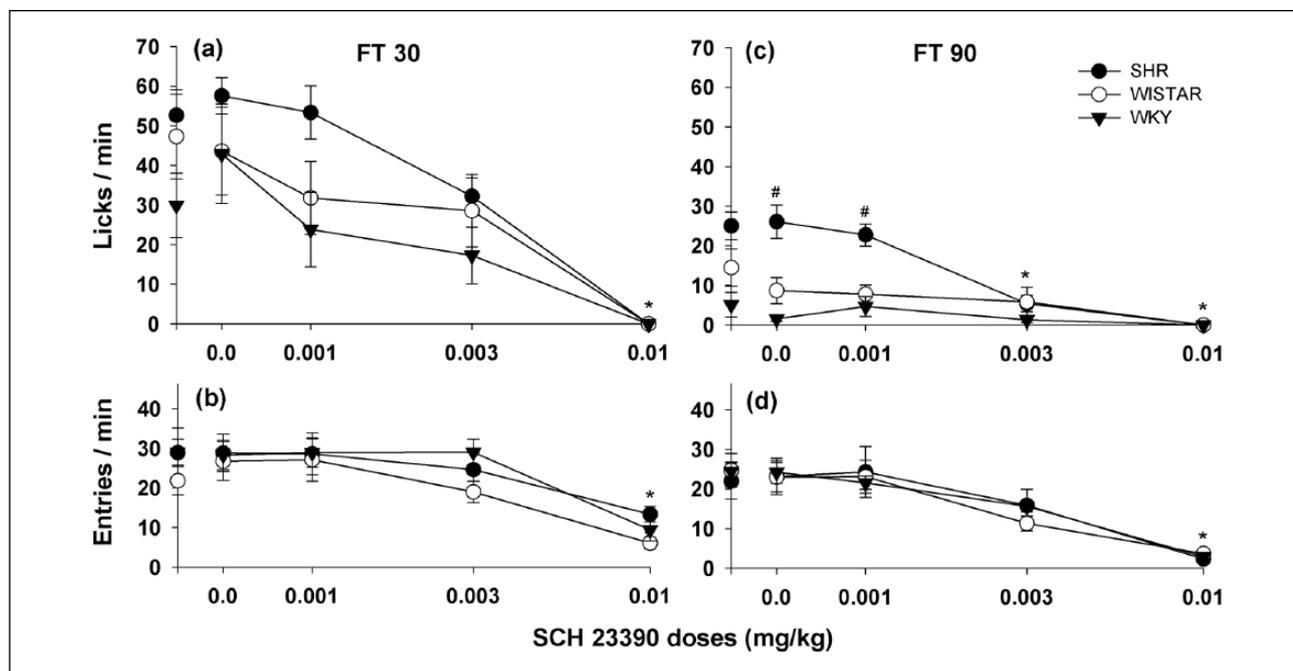


Figure 5. Dose–response functions for SCH 23390 in terms of mean (\pm SEM) licks per minute (upper panels) and mean (\pm SEM) magazine entries per minute (bottom panels) for SHR, Wistar and WKY rats during the FT 30 s (left panels) and FT 90 s (right panels) schedules. Data from the behavioural control sessions are shown over the y axis, and the doses are represented in logarithmic scale. (a) $*=p<0.05$ dose comparisons vs vehicle. (b) $*=p<0.05$ dose comparisons vs all other doses. (c) $\# = p<0.05$ for SHR vs Wistar or WKY. $*=p<0.05$ dose comparisons vs vehicle for all groups, and only for SHR at 0.003 mg/kg. (d) $*=p<0.05$ dose comparisons vs vehicle. ($N=24$.)

showing a gradual dose–dependent decrease, with differences between the highest dose of 0.01 mg/kg with respect to vehicle ($p<0.01$). Analysis of magazine entries (Figure 5(b)) revealed a ‘dose’ effect ($F(3,63)=33.93$, $p<0.01$), where the dose of 0.01 mg/kg showed decreased entries with respect to all other doses ($p<0.01$ for all comparisons).

Analysis of licks in FT 90 s (Figure 5(c)) revealed a ‘strain \times dose’ interaction ($F(6,63)=9.21$, $p<0.01$): SHRs performed more licks at the 0.001 mg/kg dose and vehicle compared to Wistar and WKY rats ($p<0.01$ in both cases). Analysis of magazine entries (Figure 5(d)) only showed a ‘dose’ effect ($F(3,63)=50.05$, $p<0.01$), with decreases observed between 0.003 and 0.01 mg/kg ($p<0.01$).

SCH 23390 was effective in all animals at reducing both licks and magazine entries, but without reliable differences between rat strains.

Eticlopride. Analysis of licks in FT 30 s (Figure 6(a)) revealed no ‘strain’ effect, but did reveal a ‘dose’ effect ($F(4,84)=38.80$, $p<0.01$), showing a gradual dose–dependent decrease, with differences between the highest dose of 0.1 mg/kg with respect to vehicle ($p<0.01$). Analysis of magazine entries (Figure 6(b)) also revealed a ‘dose’ effect ($F(4,84)=38.80$, $p<0.01$), showing a gradual dose–dependent decrease similar to that observed for licks, with differences between vehicle and the highest dose of 0.1 mg/kg ($p<0.01$).

Analysis of licks in FT 90 s (Figure 6(c)) revealed a ‘strain \times dose’ interaction ($F(8,84)=7.85$, $p<0.01$): SHR performed more licks compared to Wistar and WKY at vehicle and

the 0.001 mg/kg dose ($p<0.01$ for all comparisons). The same difference was found at the 0.003 mg/kg dose, but only in comparison to WKY ($p<0.01$). Analysis of magazine entries (Figure 6(d)) revealed no ‘strain’ effect, but revealed a ‘dose’ effect ($F(4,84)=53.20$, $p<0.01$), showing a gradual dose–dependent decrease in entries, with differences between the higher dose of 0.1 mg/kg with respect to vehicle ($p<0.01$).

Eticlopride reduced lick rates in all the animals in FT 30 s, but was less efficacious in FT 90 s for SHR. Despite this difference, eticlopride showed the same effectiveness in reducing magazine entries in all the strains and in both FT schedules.

Discussion

In the present study, three different strains of rats were submitted to a SIP procedure under two different FT schedules (see a detailed analysis of the acquisition data in Íbias et al., 2015). FT 30 s resulted in robust levels of adjunctive behaviour, with no differences between strains. During FT 90 s, SHRs successfully maintained SIP despite a reduction in the rate of food delivery, whereas Wistar and WKY rats, by comparison, developed lower levels of adjunctive drinking (see similar findings on differences between strains of rats as a function of inter-food interval length in Íbias and Pellón (2011, 2014)). Magazine entries remained constant and without differences among rat strains or between FT schedules.

The issue as to why SHRs showed higher licking than Wistar and WKY controls, but showed similar magazine entries, may rely on magazine entries being controlled by Pavlovian stimuli

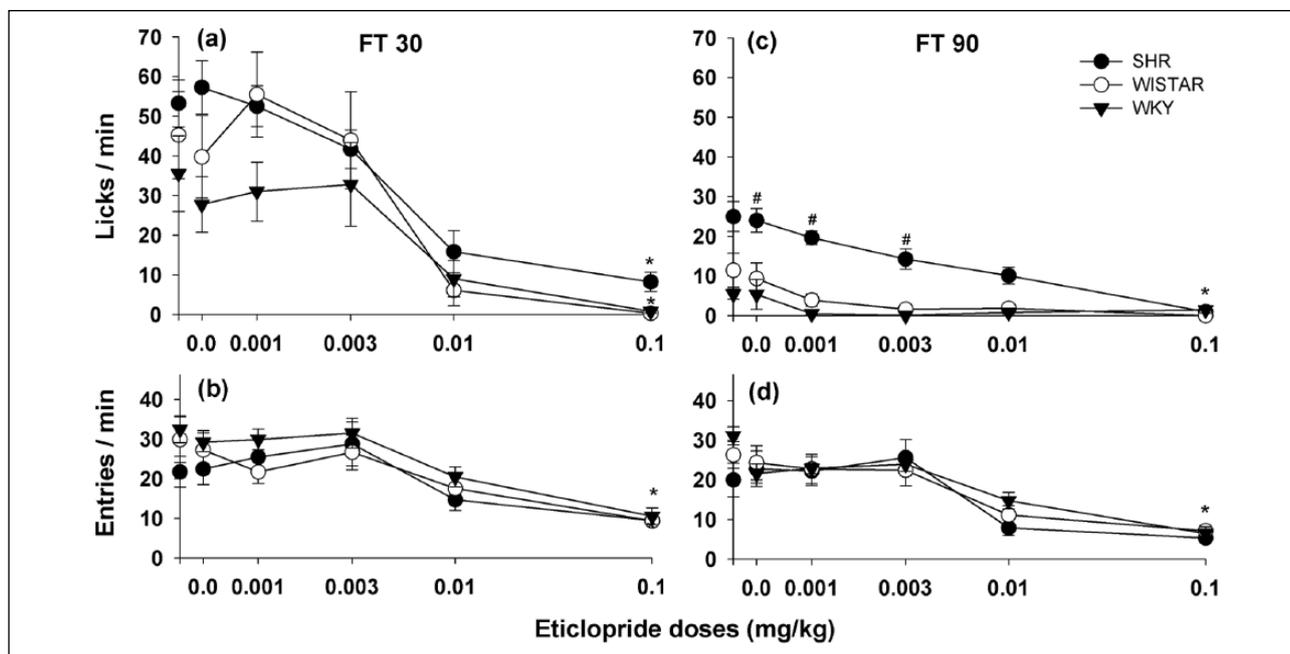


Figure 6. Dose–response functions for eticlopride in terms of mean (\pm SEM) licks per minute (upper panels) and mean (\pm SEM) magazine entries per minute (bottom panels) for SHR, Wistar and WKY rats during the FT 30 s (left panels) and FT 90 s (right panels) schedules. Data from the behavioural control sessions are shown over the y axis, and the doses are represented in logarithmic scale. (a) $*=p<0.05$ dose comparisons vs vehicle. (b) $*=p<0.05$ dose comparisons vs vehicle. (c) $\#=p<0.05$ for SHR vs Wistar or WKY, but only vs WKY at 0.003 mg/kg. $*=p<0.05$ dose comparisons vs vehicle for all groups, and vs 0.003 mg/kg just for SHR. (d) $*=p<0.05$ dose comparisons vs vehicle. ($N=24$.)

(Harris et al., 2013) that may interact with (and eventually take control of) operant contingencies operating in the initial stages of the behaviour (Pellón and Killeen, 2015). Excessive operant performance seems to be a characteristic of SHRs (Hill et al., 2012).

WKY rats, when compared to SHRs, show poor levels of motor activity (Gentsch et al., 1987; Paré, 1992), high levels of stress (Grauer and Kapon, 1993), anxiety (Carr and Lucki, 2010) and fear (Ledoux et al., 1983), and resistance to anti-depressive drugs (Lahmame et al., 1997; López-Rubalcava and Lucki, 2000), and have been proposed as an animal model of depression (Solberg et al., 2001; Will et al., 2003). In the present study, WKY rats showed similar results to Wistars, but with a trend towards earlier declines on SIP as a function of increases in drug doses.

d-AMP generally resulted in dose-dependent reductions of SIP performance that are in accordance with previous studies (Mittleman et al., 1994; Pellón and Blackman, 1992; Sanger, 1978; Williams and White, 1984; Yoburn and Glusman, 1982). We also observed that MPH decreased SIP (see also Wayner et al., 1979). In addition, whereas Wistar and WKY rats showed gradual dose-dependent reductions of SIP after administration of these compounds, SHRs showed no decrease until they were administered a dose of such magnitude that it produced an abrupt reduction. This effect appears independently of a baseline rate of licking (see Flores and Pellón, 1995), as it occurred both in FT 30 s and FT 90 s schedules, and SHR only showed a reliable higher rate of licks than Wistar and WKY rats in the FT 90 s schedule. That is, SHRs showed certain insensitivity to low to medium-range doses of d-AMP and MPH affecting the licking induced by both FT schedules. This is the first study to report the effects of d-AMP and MPH on the SIP of SHR, as well as on WKY rats.

At the highest doses of both d-AMP and MPH, the decrease of SHRs' licking was accompanied by a reduction of magazine entries. This was also observed in Wistar rats, but to a lesser degree. It is known that d-AMP reduces consummatory behaviour as a consequence of dose-dependent increases in unconditioned behaviours (Cole, 1980) and locomotor activity (Fujita et al., 2003; Hynes et al., 1985; Myers et al., 1982). In the present study, the highest doses of d-AMP and MPH could have reduced SIP and magazine entries indirectly as a consequence of increased general activation that interfered with consummatory behaviours, occasionally leading to even not consuming all of the food pellets delivered (at the highest dose of d-AMP and principally in SHR).

Since one of the action mechanisms of d-AMP and MPH is the facilitation of dopamine release into the synaptic cleft (Feldman et al., 1997), a reduced transport into the vesicles could have been a key factor involved in the low sensitivity of SHR to the effects of these drugs, a possibility supported by the impaired DA release that is shown by SHR under basal conditions (Russell et al., 1998). Moreover, the faster DA uptake that SHRs show in the ventral striatum and nucleus accumbens (Miller et al., 2012) could also explain the higher dose of d-AMP and MPH needed to reduce SIP in these animals.

In general, selective DA receptor agonists and antagonists decreased SIP performance in a dose-dependent manner, but not all of these drugs provoked exactly the same effects. Both DA D_1 and D_2 receptor antagonists (SCH 23390 and eticlopride) reduced SIP in all strains, however, only the DA D_2 receptor antagonist eticlopride was less effective in reducing licking of SHR during the FT 90 s schedule in comparison to Wistar and WKY rats. Only the DA D_2 receptor agonist quinpirole decreased SIP

without generally affecting magazine entries. Results regarding Wistar rats are comparable to a previous report from our laboratory (Pellón et al., 2007), and the testing of these DA-selective compounds is novel to the present research in relation to a SIP procedure with SHR and WKY rats.

While the DA D₁ receptor antagonist SCH 23390 reduced SIP under FT 30 s and FT 90 s schedules, such reduction was not observed after administration of the DA D₁ receptor agonist SKF 38393. However, it is important to note that the range of doses used in the present study for SKF 38393 could be below the effective dose (8.0 mg/kg as reported by Mittleman et al. (1994)). The reduction of SIP regarding DA D₂ receptor agonists and antagonists could be due to their effects on DA D₂ auto-receptors and/or D₂ postsynaptic receptors (Beaulieu and Gainetdinov, 2011). Specifically, DA D₂ receptor agonists could reduce synaptic DA by interacting with DA D₂ autoreceptors, while DA D₂ receptor antagonists could reduce dopaminergic actions by blocking the DA D₂ postsynaptic receptors. Previous results from our laboratory showed that, while DA D₂ receptors could be involved in the motor aspects of SIP, DA D₁ receptors appear to be implicated in its motivational component (Pellón et al., 2011). Notwithstanding, it is difficult to explain in terms of mechanisms why both agonist and antagonists reduced SIP. The non-specific nature of the effects of these drugs on adjunctive drinking has been previously explained as a consequence of a change in the balance of activation of DA D₁ and D₂ receptors that may contribute to alterations in DA neurotransmission (Mittleman et al., 1994). The fact that DA D₁ receptors are primarily in a low-affinity agonist state, whereas the DA D₂ receptors are primarily in a high-affinity agonist state (Richfield et al. 1989), could explain the different effects of DA D₁- and D₂-like selective compounds on SIP. Thus, higher doses of DA D₁ receptor agonists are necessary to show specific behavioural effects. Both DA D₁ and D₂ receptor antagonists produced similar effects under relatively high doses, decreasing licks and magazine entries in all animals, whereas the DA D₁ receptor agonist SKF 38393 failed to reduce drinking, and the DA D₂ receptor agonist quinpirole reduced licks but not magazine entries. On the other hand, the lower sensitivity to dopaminergic effects on SIP in the SHR could be on the basis of the altered dopaminergic function that has been previously reported in this strain (Heijtz et al., 2007; Langen and Dost, 2011; Russell, 2003). This neurochemical characteristic, critical in ADHD patients, could be indicating why higher doses of both d-AMP and MPH are needed to produce in SHR similar effects to those found in control rat populations.

Conclusions

After administering several pharmacological DA compounds on SIP in SHRs, the comparisons established between this rat model of ADHD and its controls confirmed the SHR as a reference of enhanced SIP performance. SHRs show adjunctive behaviour under circumstances that normally do not favour SIP performance in control rats (the FT 90 s schedule in the present study), and these reasonably elevated levels of adjunctive drinking, which are maintained despite decreases in food frequency, are similar to the high rate of operant responding that has been reported in SHRs under variable-interval food schedules, which, in turn, has been characterized as incentive-elicited hyperactivity (Hill et al., 2012). Based upon the differences between rats' strains among FT schedules, coupled with a differential DA reactivity, this hyperactivity

could provide an explanation for why SHR rats continue to show SIP under environmental and pharmacological challenges that normally disrupt drinking. In view of these results, the described hyperfunction in the dopaminergic system, observed in both humans with ADHD and SHRs, may be pointing towards a possible co-factor in the impairment of social skills related to the disorder: ADHD patients may be suffering, to a certain extent, from a greater intromission of adjunctive behaviours, which would interfere with target ongoing activities.

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