The Effect of Methylphenidate on the Microstructure of Schedule-Induced Polydipsia in an animal model of ADHD

Javier Íbias[a,c], Carter W. Daniels[b], Miguel Miguéns[c], Ricardo Pellón[c] and Federico Sanabria[b]

[a] *Western University of Health and Sciences, Pomona, CA, USA*
[b] *Arizona State University, Tempe, AZ, USA*
[c] *Universidad Nacional de Educación a Distancia (UNED), Madrid, Spain*

Abstract

Schedule-induced polydipsia (SIP) was established in the Spontaneously Hypertensive Rat (SHR), Wistar Kyoto (WKY) and Wistar rats, using a multiple fixed-time (FT) schedule of food delivery, with components of 30 and 90 s. Thereafter, animals were exposed to chronic methylphenidate (MPH; 2.5 mg/kg/d) immediately before each of 6 consecutive daily SIP sessions. A test to assess possible sensitization effects was also conducted four days after drug treatment. At baseline, FT 90-s produced longer and more frequent drinking episodes in SHR than in WKY. An analysis of the distribution of inter-lick intervals revealed that drinking was organized in bouts, which were shorter in SHR than in WKY. Across strains and schedules, MPH shifted drinking episodes towards the beginning of inter-food intervals, which may reflect a stimulant effect on SIP. MPH transiently reduced the frequency of drinking episodes in WKY in FT 30-s, and more permanently reduced the frequency of licking bouts in Wistar rats. MPH also increased the length of licking bouts in Wistar rats. Overall, SHR displayed a hyperactive-like pattern of drinking (frequent but short bouts), which 2.5 mg/kg MPH appears to reduce in WKY and Wistar rats, albeit not in SHR. It appears that therapeutic effects of MPH on hyperactive-like SIP require higher doses in SHR relative to control strains.

Keywords: Schedule-induced polydipsia, Methylphenidate, Attention-deficit hyperactivity disorder, Bouts, Spontaneously Hypertensive Rat, Wistar Kyoto rats.

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1. Introduction

The most common symptoms observed in the hyperactive/impulsive subtype of attention deficit hyperactivity disorder (ADHD) are both hyperactivity and an increased sensitivity to the delay of reinforcement [1,2]. The chronic administration of stimulants attenuates these symptoms [3]. In particular, methylphenidate (MPH), a norepinephrine-dopamine reuptake inhibitor, is the most common treatment to control symptoms of ADHD [4-6].

The spontaneously hypertensive rat (SHR) is a validated animal model of ADHD [7-9]. It displays most of the symptoms of ADHD, including hyperactivity [10-12], sensitivity to delay of reinforcement [13], and inattention, although inattention is observed only when reinforcers are delayed [14]. SHR hyperactivity appears to facilitate learning and persistence, which in turn facilitate the acquisition of new behaviors [15]. In fact, SHR hyperactivity is particularly noticeable in weakly reinforced responses [10]. Nonetheless, behavioral and pharmacological evidence suggests that the SHR model does not mimic the full spectrum of symptoms associated with ADHD [14,11,16].

SHR rats display an enhanced acquisition of schedule-induced polydipsia (SIP; [17,18]). SIP is the excessive drinking observed in animals that are slightly food deprived, when they have free access to water and periodic access to small quantities of food [19]. SIP is observed even if there is no arranged contingency between drinking and the delivery of the food [20]. Of particular importance to this study, SIP is considered a behavioral model of compulsive behavior [21-23].SIP emerges with varied strength under Pavlovian contingencies [24], but their rate of occurrence and their distribution seem to be governed by operant rules underlying both their development and maintenance [25]. The drinking behavior of SHR when access to food is periodic is consistent with the instrumental basis of

SIP. When comparing SHR against control strains, differences in the distribution of inter-lick intervals (ILIs) during SIP are similar to differences in the distribution of instrumental inter-response times [10,26].

Previous work indicates that ILIs during SIP are well described by the Biexponential Refractory Model (BERM) of free-operant performance [27,28]. According to this model, subjects fluctuate in and out of drinking bouts such that three parameters characterize the distribution of ILIs: the rate at which licking bouts are initiated (b), the rate of licking within bouts (w), and the probability that a lick is not the last one in a bout [p; mean licking bout length = $1/(1-p)$ licks]. Expressed mathematically,

$$\begin{aligned} &P(ILI = t \mid t < \delta) = 0 \\ &P(ILI = t \mid t \geq \delta) = pwe^{-w(t-\delta)} + (1-p)be^{-b(t-\delta)} \end{aligned} \quad 0 \leq p \leq 1; b \geq w > 0; \delta > 0 \quad (1)$$

Equation 1 assumes that there is a minimum time between consecutive licks, δ, that characterizes the motoric capacity to produce licks. This equation states that some ILIs (those within licking bouts) are sampled, with probability p, from an exponential distribution with mean $1/w$, and other ILIs (those separating licking bouts) are sampled, with probability $1-p$, from an exponential distribution with mean $1/b$.

The present study tested the effects of a chronic therapeutically relevant dose of MPH (2.5 mg/kg; [29]) on SIP in SHR. Effects on SHR were compared to those on Wistar and Wistar Kyoto (WKY) rats. WKY rats are the normotensive control of SHR but, in view of their elevated levels of fear and anxiety [30,31] and resistance to antidepressant drugs [32,33], are also used as an animal model of depression[34,35].

A previous study [36] failed to find an effect of an acute administration of 2.5 mg/kg MPH on lick rate and food-seeking behavior in a SIP procedure in SHR and Wistar rats. In the present study, exposure to 2.5 mg/kg/d of MPH was extended to 6 d, and performance was analyzed at a microstructural level. The development of tolerance to MPH was assessed using a sensitization test [37] four days after the end of chronic treatment. Behavior analysis was thus conducted at two levels: a molar level, focused on the temporal distribution of SIP episodes, and a molecular level, based on BERM and focused on the temporal distribution of individual licks.

2. Method

2.1.Subjects

Eighteen male rats of three strains—8 SHR, 6 WKY and 5 Wistar—obtained from Charles River Laboratories (Barcelona, Spain) were used. They were housed singly in 18.0 x 32.5 x 20.5 cm transparent Plexiglas cages with a metal-grid roof, located in an environmentally-controlled room with a 12-hour light-dark cycle (lights on at 08:00 h), ambient temperature of 17 ºC to 23 ºC, and 45% relative humidity.

Prior to the current procedure, SIP was induced and evaluated in all animals after 40 acquisition sessions (see Íbias et al. (2015) [26] for a detailed description of SIP acquisition), using the behavioural treatment described below in the procedure section. In addition, all the rats were exposed to identical acute drug treatments using several dopaminergic compounds after SIP acquisition. Drug treatment previous to this study was not expected to affect the current procedure, as any carryover effect was minimized by allowing no more than two drug administrations per week, always flanked by rest days, and

demonstrated by the full recovery of baseline performance after 48 h of drug discontinuation (see Ibias et al. (2016) [36] for further details).

Rats were 36 weeks old at the start of the present experiment. Their average weights were 307 g (SHR; range: 299-323 g), 345 g (WKY; range: 310-362 g), and 356 g (Wistar; range: 343-368 g). Weights were reduced in proportion to standard growth curves for each strain to 80%-85% of free-feeding weight by a controlled diet maintained throughout the experiment. Supplemental feeding was provided daily, no earlier than 20 min after the end of each experimental session.

2.2.Apparatus

Eight Letica LI-836 conditioning chambers, measuring 29 x 24.5 x 35.5 cm, enclosed in soundproofed housing, each equipped with its own ventilation and a small observation window at the front. A water bottle was fitted on the exterior of the right-hand wall of the chamber, and the rat had access to the spout from the interior of the chamber (see Íbias et al. (2015) [26] for a detailed description). On each lick, 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. Licks were recorded at a resolution of 0.1 s using MED-PC IV (Med Associates, St. Albans, VT, USA). Forty-five mg food pellets (Bio-Serv, Frenchtown, NJ, USA) could be dispensed in an aperture in the chamber's front wall. The chambers were lit by an indirect 25-W light, and by two 3-W lamps situated on the front panel. A fan that produced an ambient noise of approximately 60 dB in each chamber masked exterior sound. Each chamber had a speaker that produced auditory stimuli when necessary.

2.3.Procedure

2.3.1. Behavioral procedure

Drinking was induced using a multiple fixed-time (FT) 30-s FT 90-s schedule, with components signaled by the presence or absence of a 65-dB, 4.5 Hz tone. Tone assignment was counterbalanced across FT components and across rats within each strain. In each component, a food pellet was delivered every 30 s (FT 30-s) or every 90 s (FT 90-s), regardless of the behavior of the animals. Rats were given 40 food pellets per session, 20 in each component; the lights of the experimental chamber remained off for 60 s between FT components. Both licks and amount of water consumed were recorded.

2.3.2. Pharmacological procedure

Rats received a 1 ml/kg intraperitoneal (i.p.) injection once daily, 15 min before each experimental session. Saline (vehicle) was injected on the first day; MPH (2.5 mg/kg; Rubió Laboratories, Barcelona, Spain) was injected on the following six days (MPH sessions), and once again four days later (sensitization test). MPH was dissolved in 0.9% saline.

2.4.Statistical analysis

SIP performance data was analyzed separately in each FT component, using a 3 x 5 mixed-design ANOVA with factors *strain* (SHR, WKY and Wistar), and *session* (Vehicle, Day 1, Day 3, Day 6 and Sensitization test). Dependent variables included in this analysis were rate of licking, proportion of inter-food intervals with a drinking episode (2 or more licks), median latency to start drinking episodes, and median duration of drinking episodes. The temporal distribution of licks was analyzed by taking the mean number of licks on every 1-s interval bin within the inter-food interval. Separate 5 (*sessions*) x 30 or 34 (*bins*) repeated-measures ANOVA were conducted on each FT and strain (the last 56 bins in FT 90-s were not analyzed because they were virtually always empty).

Parameters of the distribution of inter-lick intervals (ILIs) within each drinking episode during vehicle and MPH sessions were also analyzed using ANOVA [26]. It was first verified that ILIs in each condition were distributed according to the mixture of two exponential distributions—one for the interval between licking bouts and another for the ILIs within bouts. Three parameters were then computed: the rate at which licking bouts were initiated (*b*), the rate of licking within bouts (*w*), and the probability that a lick was not the last in a bout (*p*). For this analysis, MPH days were pooled and compared against data from the vehicle and sensitization tests. For all rats included in analysis, parameter estimates were obtained for each condition using the method of least squares with δ equal to the minimum IRT (in most cases δ = 0.10 s and was thus not subjected to analysis). In every condition, rats that produced fewer than 3 ILIs were excluded from analysis. One Wistar rat in the MPH condition and 3 WKY rats in the MPH and sensitization conditions were excluded on that basis of this criterion in at least one FT component. Parameter estimates obtained from the vehicle session were compared among strains and FT components using a 3 (*strain*) x 2 (*FT schedule*: FT 30-s, FT 90-s) mixed-designed ANOVA. A 2 (*strain*: SHR, Wistar) x 2 (*FT schedule*) x 3 (*condition*: vehicle, MPH, sensitization) ANOVA was also conducted on parameter estimates to assess their sensitivity to MPH; WKY rats were excluded from this analysis because too few passed the inclusion criterion in the MPH and sensitization conditions. The lowest p-value reported in every analysis was 0.01, with α = 0.05. All analyses were conducted using SPSS 19 © Software.

3. Results

Fig. 1A shows the mean (±SEM) licks/min through the first, third, and sixth MPH session, and the sensitization test, for the three strains of rats in the FT 30-s schedule. A significant *strain* x *session* interaction effect was obtained [$F(8,64)= 2.19$, $p<0.01$]. Post hoc comparisons revealed a reduced licking rate in WKY rats in the first and third MPH sessions, as well as in the sensitization test; the effect of MPH was observed relative to SHR in all these sessions ($p<0.01$ in all comparisons), relative to Wistar rats only in the first session ($p<0.03$), and relative to vehicle in the first session and the sensitization test ($p<0.01$ for both comparisons). This pattern of results suggests that MPH suppressed SIP, but only in WKY, that tolerance to this effect was developed over repeated daily injections, and that 4 d of rest were sufficient to recover from tolerance. Fig. 1B shows analogous data for the FT 90-s schedule. In this schedule, SHR showed higher rates of licks compared to WKY as revealed by a significant *strain* effect [$F(2,16)= 14.75$, $p<0.01$].

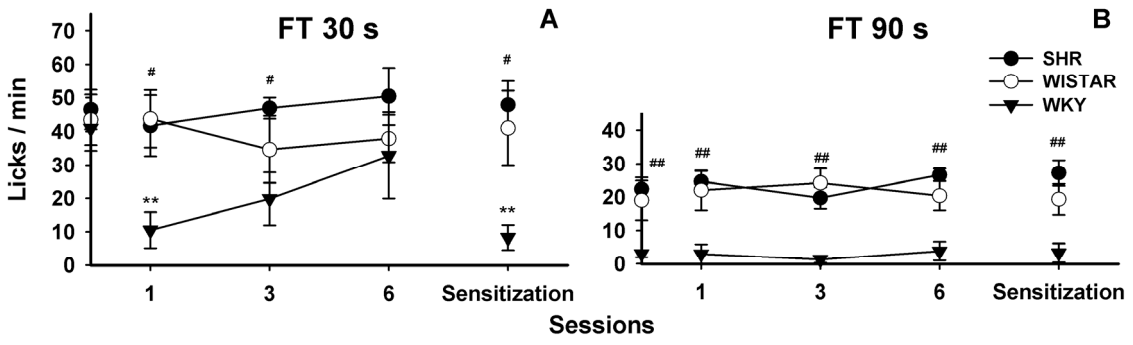

Fig. 1. Mean (±SEM) licking rate in the first, third, and sixth MPH session, and the sensitization test, for the three strains of rats in the FT 30-s (Fig. 1.A) and FT 90-s (Fig. 1.B) schedules. Data from vehicle sessions are presented on the Y axes. In FT 30-s, MPH reduced SIP in WKY rats, but tolerance to such effect appears to develop; in FT 90-s, WKY displayed reduced SIP, regardless of condition. $^{\#\#}$ = $p<0.01$ strain comparisons. * = $p<0.05$ intra-group comparisons. (N =19).

Fig. 2.A shows the mean (±SEM) proportion of trials with a drinking episode (at least 2 licks within a IFI) in FT 30-s for each strain. A significant *strain* x *session* interaction effect was observed [$F(8,64)= 2.76$, $p<0.02$]. Post hoc comparisons revealed fewer drinking episodes in WKY in the first and third MPH sessions, as well as in the sensitization test; the effect of MPH was observed relative to SHR and vehicle in all these sessions ($p<0.01$ for all comparisons), and relative to Wistar rats during the first session ($p<0.01$). Fig. 2.B shows analogous data for the FT 90-s schedule. A significant *strain* effect [$F(2,16)= 5.26$, $p<0.01$] revealed that SHR and Wistar rats made more drinking episodes than WKY in this schedule ($p<0.01$ for both comparisons).

Figs. 2.C and 2.D show the mean (±SEM) latency to initiate drinking episodes in FT 30-s and FT 90-s, respectively, for each strain. A significant *session* effect was observed in both schedules [FT 30-s: $F(4,52)= 8.03$, $p<0.01$; FT 90-s: $F(4,48)= 6.10$, $p<0.01$]. Shorter latencies were observed in the first ($p<0.01$ in both comparisons) and sixth ($p<0.03$ in FT 30-s, $p<0.01$ in FT 90-s) MPH sessions, as well as in the sensitization test ($p<0.01$ in both comparisons), when compared to vehicle sessions. In general, MPH reduced the latency to start SIP episodes, when these were observed, in all animals.

Fig. 2.E shows the mean (±SEM) duration of the SIP episodes in FT 30-s for each strain. No significant effect of *strain* or *session* was observed. Fig. 2.F shows analogous data for the FT 90-s schedule. A significant *strain* effect [$F(2,11)= 4.74$, $p<0.03$] revealed that, compared to SHR, WKY rats produced SIP episodes of shorter duration.

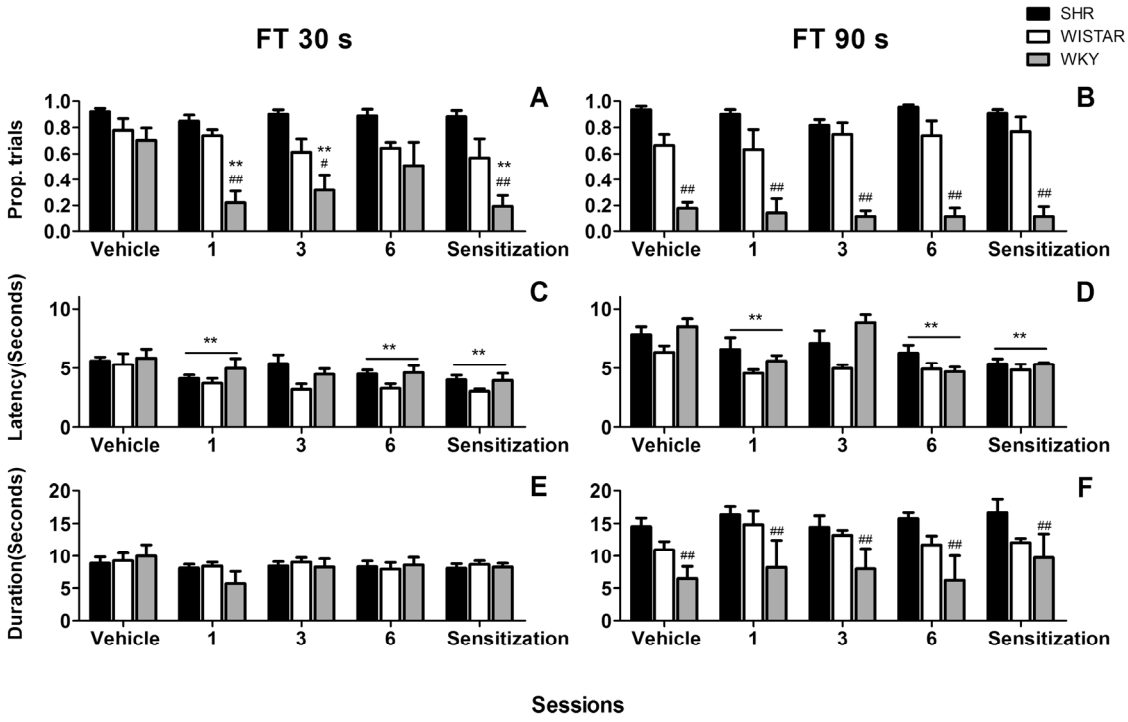

Fig. 2. Mean (±SEM) (A) proportion of trials with a drinking episode (at least 2 licks) in FT 30-s and (B) FT 90-s (*N*=19); (C) latencies to initiate drinking episodes in FT 30-s (*N*=15) and (D) in FT 90-s (*N*=14); (E) duration of SIP episodes in FT 30-s (*N*=15) and (F) FT 90-s (*N*=14). MPH reduced the latency to initiate drinking episodes regardless of strain and schedule, but it also reduced the number of drinking episodes in WKY in FT 30-s. In FT 90-s, WKY emitted fewer and shorter drinking episodes. # = p<0.05 strain comparisons. ## = p<0.01 strain comparisons. * = p<0.05 intra-group comparisons. ** = p<0.01 intra-group comparisons.

Fig. 3 shows mean (±SEM) licks in each 1-s bin as a function of time in FT 30-s, analyzed separately for each strain. A significant *bin* x *sessions* interaction effect was observed on SHR performance [Fig 3.A; $F(116,196)= 1.62$, $p<0.01$], with differences between vehicle and both the last MPH and the sensitization sessions in bin 4 ($p<0.05$ for both comparisons), and differences between vehicle and all the other sessions in bins 5 and 6, except for vehicle and the first MPH session in bin 6 ($p<0.05$). A significant *bin* x *sessions* interaction effect was also observed on Wistar performance [Fig. 3.B; $F(116,464)=$

2.42, $p<0.01$]; differences were observed between vehicle and the first MPH session in bins 13 and 14, between vehicle and the third MPH session in bins 12 and 13, between the third MPH session and sensitization session in bin 15, and also between vehicle and sensitization session in bins 13, 14, and 15 ($p<0.05$ for all comparisons). A significant *bin* x *session* interaction effect was observed on WKY performance [Fig. 3.C; $F(116,580)= 3.57$, $p<0.01$]. Relative to vehicle, differences were observed in the first MPH session in bins 12, 15-17, and 19; in the third MPH session in bins 9, 10, 12, and 15-17; in the sixth MPH session in bins 12 and 15, and in the sensitization test in bins 10-18 ($p<0.05$ for all comparisons). Both SHR and Wistar showed a shift in licking rate toward the beginning of the interval as chronic MPH treatment progressed, with more noticeable effects observed during the sensitization test. WKY showed a similar pattern than Wistar rats, but adjunctive drinking decreased instead of shifting toward the beginning of the interval.

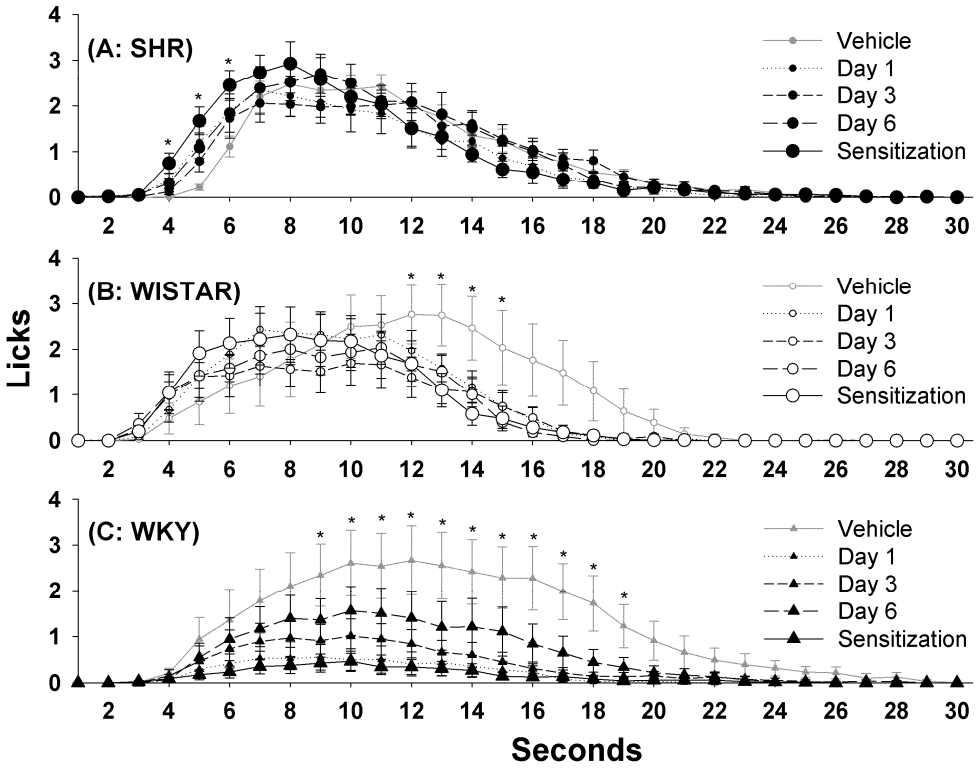

Fig. 3. Mean (±SEM) licks in each 1-s bin, for each strain during vehicle session, days 1, 3 and 6 of MPH, and Sensitization session (4 days after the end of MPH chronic treatment) in FT 30-s. *= p<0.05. A: SHR (n=8). B: Wistar (n=5). C: WKY (n=6).

Fig. 4 shows mean (±SEM) licks in each 1-s bin as a function of the first 34 s in FT 90-s, analyzed separately for each strain. A significant *bin* x *sessions* interaction effect was observed on SHR performance [Fig. 4.A; $F(132,924)= 1.82$, $p<0.01$], with differences between the vehicle session and all the other session in bins 5, 6, and (expect the third MPH session) 7, and differences between vehicle and the sensitization test also in bins 4, and 8 ($p<0.05$). No significant effects of MPH were observed on Wistar (Fig. 4.B) and WKY (Fig. 4.C) rats.

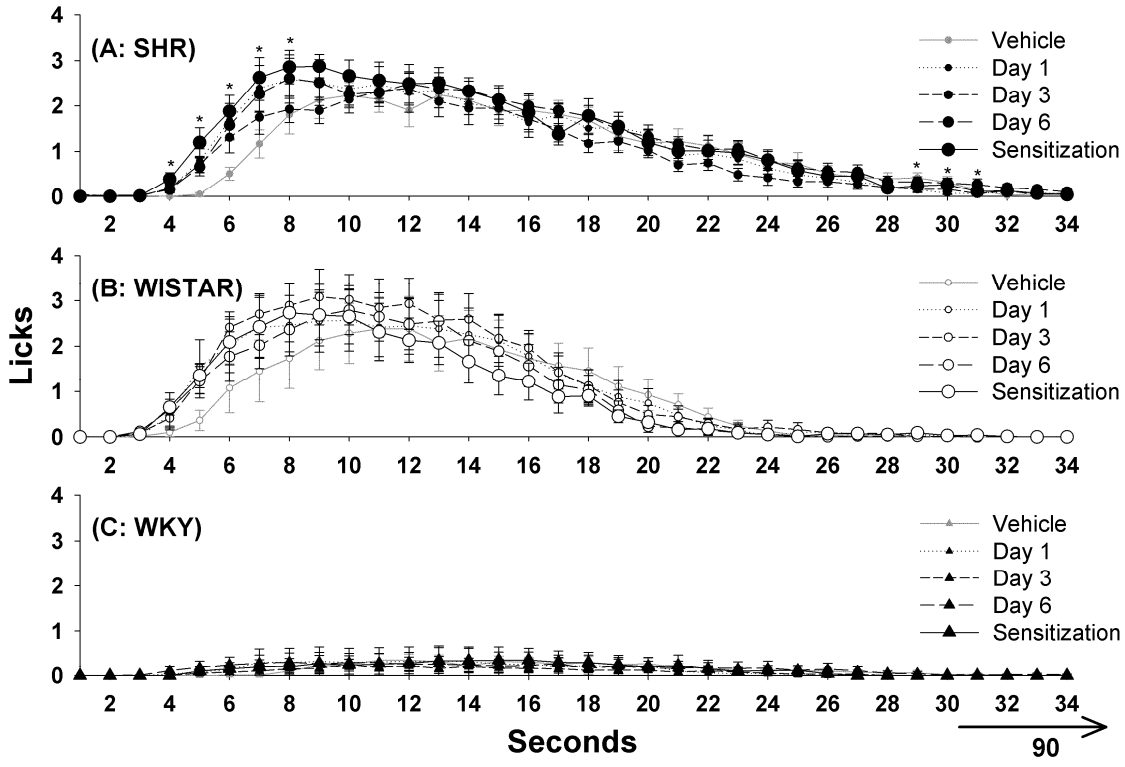

Fig. 4. Mean (±SEM) licks given in each 1-s bin, for each strain during vehicle session, days 1, 3 and 6 of MPH, and Sensitization session (4 days after the end of MPH chronic treatment) in FT 90-s. *= $p<0.05$. A: SHR (n=8). B: Wistar (n=5). C: WKY (n=3).

Fig. 5 shows fits of BERM to vehicle performance of a representative rat of each strain. Overall, fits of BERM appear adequate, suggesting that ILIs within each drinking episode were distributed according to the mixture of two exponential distributions.

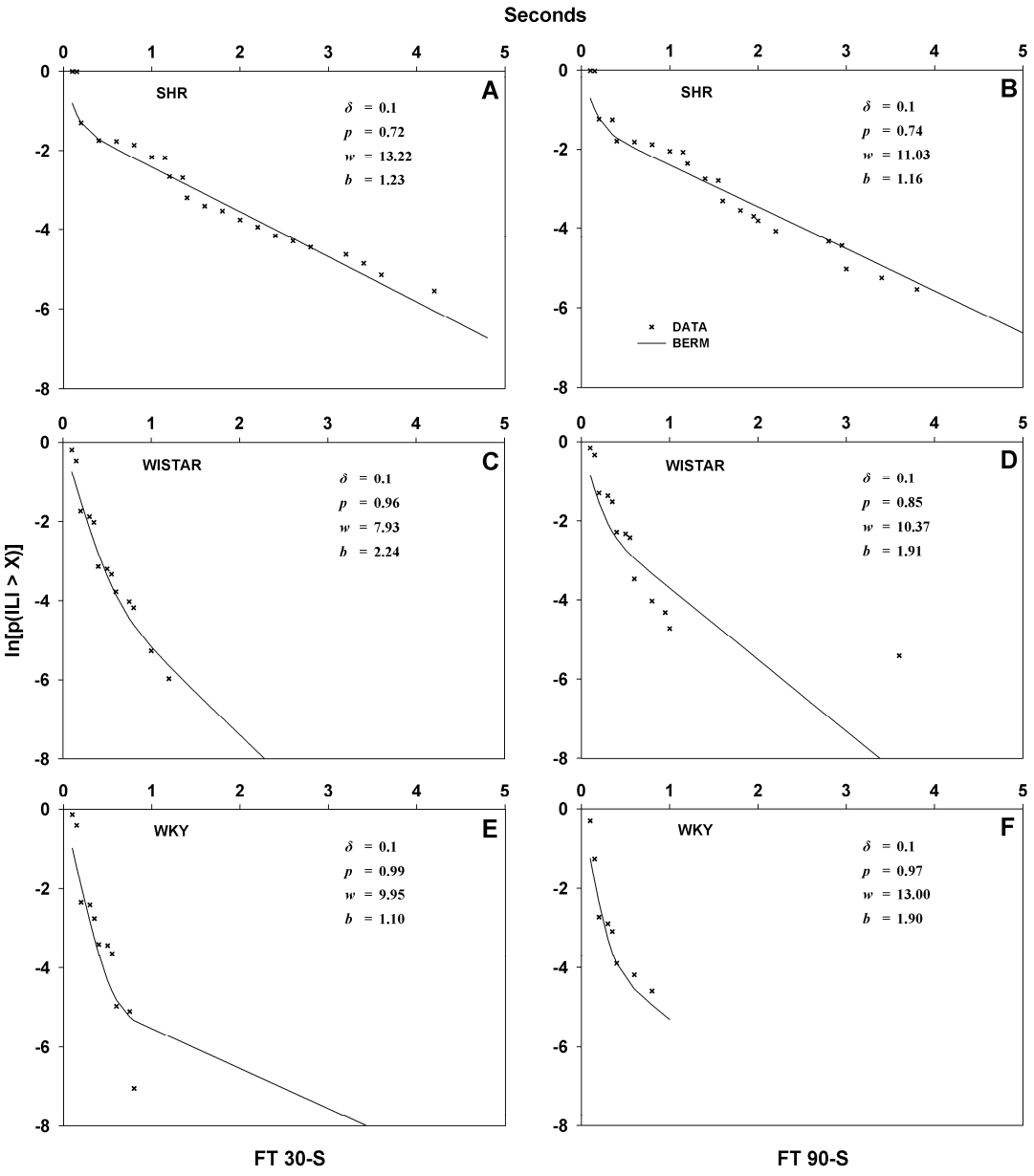

Fig. 5 Sample fits of BERM (Eq. (1); continuous curves) to individual log-survival plots of vehicle-session ILIs from selected SHR (top panels), Wistar (middle panels), and WKY rats (bottom panels). Selected rats produced the median number of licks of their strain under vehicle (FT 30-s on the left, FT 90-s on the right). Each panel includes BERM parameter estimates; BERM provided an adequate account of individual SIP performance.

Table 1: Mean (± SEM) BERM Parameter Estimations

		FT 30 s			FT 90 s		
		Condition			Condition		
Strain	Param.	Vehicle	MPH	Sens.	Vehicle	MPH	Sens.
SHR	*p*	.82 (.05)	.72 (.11)	.84 (.03)	.86 (.03)	.89 (.03)	.84 (.03)
	w	14.17 (3.01)	10.12 (1.33)	14.10 (2.53)	14.24 (2.75)	9.97 (2.52)	14.01 (2.76)
	b	1.23 (.20)	1.74 (0.32)	1.37 (0.21)	0.75 (0.20)	0.68 (0.15)	1.12 (0.26)
WIS	*p*	.89 (.03)	.95 (.03)	.93 (.05)	.92 (.03)	0.97 (.02)	.96 (.03)
	w	12.81 (3.34)	12.78 (0.92)	11.81 (1.23)	10.20 (1.58)	9.68 (1.33)	9.63 (0.81)
	b	4.89 (2.17)	2.01 (0.92)	3.09 (0.96)	1.95 (0.69)	0.21 (.09)	0.20 (0.09)
WKY	*p*	0.99 (.01)			.97 (.01)		
	w	9.45 (2.6)			11.26 (3.74)		
	b	1.10 (0.70)			1.94 (.81)		

Note. Param = Parameters, MPH = Methylphenidate, and Sens. = Sensitization. Parameter δ is not shown or analyzed because for all but two rats, δ = .010 s. Parameters *w* and *b* are expressed in licks/s. WKY were omitted from the analysis of MPH sessions and the sensitization test because not enough data were available for the reliable estimation of parameters.

Table 1 shows mean (± SEM) BERM parameter estimates (Eq. 1) for all three strains, under each FT schedule. A first analysis included data from all strains under vehicle. This analysis revealed a significant main effect of strain on estimates of *p* [$F(2,14)= 9.12$, $p<0.01$]. Post hoc tests revealed a significantly lower *p* (shorter licking bouts) in SHR relative to WKY ($p<0.01$).

A second analysis included data from SHR and Wistar rats under all conditions. In this analysis, estimates of *p* were larger (i.e., licking bouts were longer) under FT 90-s

compared to FT 30-s [$F(1,10)= 5.69$, $p<0.04$]. A significant *condition* × *strain* interaction effect [$F(2,20)= 4.67$, $p<0.05$] was also found on estimates of parameter *p*. Probe ANOVAs indicated that *p* was significantly lower in SHR than in Wistar rats in MPH sessions [$F(1,11)= 12.37$, $p<0.01$] and in the sensitization test [$F(1,11)= 5.98$, $p<0.01$], and also indicated a significant effect of *condition* in Wistar rats [$F(2,8)= 7.49$, $p<0.02$]. Post hoc tests revealed that estimates of *p* increased for Wistar rats between vehicle and MPH sessions ($p<0.02$). Estimates of *w* were larger (i.e., rates of within-bout licking were higher) under FT 30-s than FT 90-s [$F(1,10)= 5.28$, $p<0.05$]. Significant *FT schedule* x *strain* [$F(1,10)= 11.55$, $p<0.01$] and *condition* x *strain* [$F(2,20)= 15.87$, $p<0.01$] interaction effects were observed on estimates of parameter *b*. Estimates of *b* were larger under FT 30-s than under FT 90-s. Probe ANOVAs revealed that estimates of parameter *b* declined in FT 90-s in SHR rats [$F(1,7)= 20.91$, $p<0.01$], and also revealed a significant effect of *condition* in Wistar rats [$F(2,8)= 3.30$, $p<0.05$]. Estimates of parameter *b* declined between vehicle and MPH sessions in Wistar rats ($p<0.05$). Taken together, this analysis shows that SHR rats emit shorter licking bouts than control strains, and that MPH lengthens and reduces the frequency of licking bouts in Wistar rats.

4. Discussion

The present study sought to examine the effect of the repeated administration of a therapeutically relevant dose of MPH (2.5 mg/kg) on SIP, a behavioral model of compulsive behavior, in SHR, an animal model of ADHD. At baseline, feeding at long periods (90 s) produced longer and more frequent drinking episodes in SHR than in a control WKY strain (Figs. 1B, 2B, and 2F). During these drinking episodes, and regardless of food periodicity, rats engaged in bouts of licking (Fig. 5). These bouts were shorter in

SHR than in WKY (Table 1, parameter *p*). This pattern of frequent drinking in short bouts displayed by SHR is remarkably similar to the pattern of frequent lever pressing for food in short bouts also displayed by this strain, which Hill et al. (2012) labeled *operant hyperactivity*. Differences in baseline SIP across strains were also observed earlier in training when food was presented every 90 s, as reported in Íbias et al. (2015) [26]. This suggests that hyperactive-like SIP is relatively stable in SHR.

There was no evidence, however, of therapeutic effects of MPH on SHR SIP. MPH did not reduce the frequency of drinking episodes in SHR; MPH only reduced it in WKY, and only transiently when food was frequently presented (Figs. 1A and 2A). MPH did not increase the length of drinking bouts of SHR either; MPH only increased it in Wistar rats (Table 1, parameter *p*). Moreover, MPH reduced the frequency of licking bouts in Wistar rats (Table 1, parameter *b*). Taken together, these findings suggest that MPH reduces hyperactive-like SIP in normoactive rats, but not in the model of ADHD.

Despite the weak or null effects of MPH on the drinking episodes of SHR, latencies to initiate those episodes were sustainedly shortened about as much in SHR as in control strains (Figs. 2C, 2D, 3, and 4). This effect suggests that the processes governing latencies are dissociable from those governing the microstructure of drinking episodes. Perhaps the former are sensitive to the stimulant effects of 2.5 mg/kg MPH (to which adult SHR and control strains are similarly responsive [38]), whereas the latter are sensitive to the therapeutic effects on MPH on ADHD-like behavior. The weak or null therapeutic effect of 2.5 mg/kg MPH on SHR SIP suggests that these effects require higher doses of MPH in SHR relative to control strains. Íbias et al. (2016) [36] showed, for instance, that SIP declines in SHR with MPH doses ranging between 5 and 10 mg/kg (although food seeking behavior also declines within this dose range). The impaired dopaminergic function showed

by adults with ADHD seem to be due to an increase in dopamine transporter (DAT) density [39,40], which in turn reduces the efficacy of dopaminergic compounds when compared to controls. This characteristic has also been observed in SHR rats.

5. Conclusion

This study replicated the hyperactive-like pattern of SIP—frequent but short bouts of drinking—observed in SHR in past studies [26]. Although SHR SIP was sensitive to a therapeutically relevant dose of MPH in some respects—inducing shorter latencies to drinking episodes—it did not yield a therapeutic effect in this strain. Positive effects in a control strain—Wistar rats—suggest that higher doses of MPH may be required to ameliorate hyperactive-like SIP in SHR. Validation of this hypothesis would support the use of SHR as a model of ADHD-related hyperactivity associated with rewards, and would support SIP as a method to assess such hyperactivity.

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