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Adult female rats' altered diurnal locomotor activity pattern following chronic methylphenidate treatment

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Abstract Methylphenidate (MPD) is one of the most prescribed pharmacological agents, which is also used for cognitive enhancement and recreational purposes. The objective of this study was to investigate the repetitive dose–response effects of MPD on circadian rhythm of locomotor activity pattern of female WKY rats. The hypothesis is that a change in the circadian activity pattern indicates a long-lasting effect of the drug. Four animal groups (saline control, 0.6, 2.5, and 10.0 mg/kg MPD dose groups) were housed in a sound-controlled room at 12:12 light/dark cycle. All received saline injections on experimental day 1 (ED 1). On EDs 2–7, the control group received saline injection; the other groups received 0.6, 2.5, or 10.0 mg/kg MPD, respectively. On ED 8–10, injections were withheld. On ED 11, each group received the same dose as EDs 2–7. Hourly histograms and cosine statistical analyses calculating the acrophase (ϕ), amplitude (A), and MESOR (M) were applied to assess the 24-h circadian activity pattern. The 0.6 and 2.5 mg/kg MPD groups exhibited significant ($p < 0.05$) change in their circadian activity pattern on ED 11. The 10.0 mg/kg MPD group exhibited tolerance on ED 11 and also a significant change in activity pattern on ED 8 compared to ED 1, consistent with withdrawal behavior ($p < 0.007$). In conclusion, chronic MPD administration alters circadian locomotor activity of adult female WKY rats and confirms that chronic MPD use elicits long-lasting effects.

Keywords Ritalin · Circadian rhythm · Behavior

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Introduction

The circadian rhythm regulates many aspects of mammalian physiology and behavior and is an integral part of life for all bodily functions. It is seen in a range of life forms from the subcellular organelles to the complex human body (Welsh et al. 1995, Moore 1983). The suprachiasmatic nucleus (SCN) is widely accepted as the master clock (Moore 1983; Reid and Burgess 2005; Sujino et al. 2003; Yamazaki et al. 2000) and expresses several clock genes such as Per1, Per2, Cry1, Cry2, bmal1, and Rev-erb (Klein et al. 1991; Reppert and Weaver 2002). This master clock also dictates the circadian rhythm and synchronizes multiple internal clocks governing physiological processes such as hormonal release, heart rate, blood pressure, eating pattern, and sleep/wake cycle (Bittman et al. 2003; Janssen et al. 1994; Mistleberger 2005) by entraining to the light/dark cycle via the retinohypothalamic tract (Benstaali et al. 2001; Cermakian and Sassone-Corsi 2002; Johnson et al. 1988; Moore and Lenn 1972). In addition to environmental cues, pharmacological agents such as psychostimulants have been shown to have effects on diurnal activity differences. For example, chronic EtOH alters Per1 and Per2 gene expression in hypothalamus and Per2 and Per3 in SCN (Chen et al. 2004; Manev and Uz 2006) causing sleep–wake abnormalities and depression (Vitaterna et al. 2001). Methamphetamine alters striatal Per1 and Per2 genes causing a shift from nocturnal to diurnal rhythms (Iijima et al. 2002). Methylphenidate has been shown to delay the SCN electrical activity, resulting in altered sleep and circadian rhythmicity (Antle et al. 2012). Disruption of circadian rhythm can result in short-term conditions, such as jet lag, fatigue, and insomnia, and contribute to long-term pathologies such as diabetes mellitus, heart disease, and hypertension (Bray and Young 2007; Filipski et al.

2002; Karlsson et al. 2001; Lamont et al. 2007). In addition, changes in circadian rhythmic activity serve as experimental markers in animals to correlate with long-term effects of psychostimulant in humans (Algahim et al. 2009; Bergheim et al. 2012; Glaser et al. 2012; Lee et al. 2011).

Methylphenidate hydrochloride is a central nervous system stimulant resembling in structure to dextroamphetamine (Kallman and Isacc 1975, Patrick and Markowitz 1997). The d-enantiomer is pharmacologically active, but the l-enantiomer does cross the blood–brain barrier contrary to prior belief (Ding et al. 2004). When MPD is given intravenously, it binds to DA transporter (DAT) and prevents the reuptake of DA to the presynaptic terminal, resulting in the accumulation of DA in the synaptic cleft (Izenwasser et al. 1999; Massello and Carpenter 1999; Patrick and Markowitz 1997; Volkow et al. 1999). Cross sensitization between MPD and cocaine was reviewed by Gatley et al. (1999), citing 26 animal studies supporting the similarity between the two stimulants in terms of drug discrimination, self-administration, locomotor activity, and other specific behaviors, while six opposing animal studies were also reviewed. MPD, or better known through its trade name Ritalin, is currently the most prescribed treatments for attention deficit and hyperactive disorder (ADHD) according to the CDC report (2011). Moreover, MPD is gaining popularity among college students as well as middle-age adults without the diagnosis of ADHD as a cognitive enhancer and for recreational usage (Greely et al. 2008; Stix 2009). A 2005 survey of US college-age students shows that 7 % have used stimulant for "non-medical" reason at least once (McCabe et al. 2005).

This experiment aims to study the long term effect of acute and chronic MPD dose response exposure on adult female Wistar–Kyoto (WKY) rats. Female rats have mainly been excluded from studies due to their more complex reproductive system than males. It is reported that responses to morphine, amphetamine, and cocaine are stronger in females than males in animal models and humans (Brecht et al. 2004; Hernandez-Avila et al. 2004; Lynch 2008). It is reported that gender and strain affect the responses to psychostimulants (Chelaru et al. 2012; Dafny and Yang 2006; Kelly et al. 1999; Melnick and Dow-Edwards 2001). To our knowledge, no prior studies have been done on adult female WKY rats. This strain was chosen as the study subject in contrast to other strains, such as Sprague–Dawley (SD) or spontaneously hypertensive rats (SHR), for genetic variation. The immediate effects of MPD on WKY, SHR, and SD rats were reported (Amini et al. 2004; Yang et al. 2003); however, none was reported on the long-term effect of MPD on WKY rats. This study will close the gap. The hypothesis is that alteration in the circadian activity pattern after chronic drug exposure indicates that the drug does exert long-term effect. The objective of this study is to confirm the above hypothesis by recording the effect of acute and chronic MPD on circadian activity pattern of adult WKY female rats for 11 consecutive days.

Methods

Animals

Female adult WKY rats ($N = 32$) weighing from 200 to 250 g were housed as four rats per cage. The cages were in a sound-controlled room with ambient temperature of 21 ± 2 °C and a relative humidity of 37–42 %. In addition, food pellets and water were supplied ad libitum throughout the experiment. The experimental room was maintained on a 12:12 light/dark schedule (light on at 0600). Animals were housed in the same test cages for 7 days for acclimatization to internally synchronize their neuroendocrine systems. On the last day of the naturalization, rats were weighed and randomly divided into one control group and three treatment groups. The groups are as follow: saline (control, $n = 8$), 0.6 mg/kg MPD ($n = 8$), 2.5 mg/kg MPD ($n = 8$), and 10.0 mg/kg MPD ($n = 8$). The animals were individually housed in the test cages (these test cages became their home cages), and an additional 24 h of accommodation was allowed before locomotor activity recording was begun.

Experimental cages

The experimental protocol has been described in detail (Gaytan et al. 1997, Yang et al. 2003, 2011). In short, open field boxes (40.5 × 40.5 × 31.5 cm each) were used, which were equipped with two levels of 16 infrared beams with their motion sensors. These were placed 6 and 12 cm from the cage floor, respectively. A computerized animal activity monitoring (CAAM; AccuScan Instruments, Inc., Columbus Ohio) system checked each sensor beam at a frequency of 100 Hz to determine whether beams were interrupted. The interruption of any beam was recorded as an activity score; cumulative counts were compiled and downloaded every 10 min into OASIS data collection program that differentiated these events into various locomotor activity indices.

Drugs

Methylphenidate (MPD) hydrochloride was dissolved in 0.9 % saline and dosages calculated as freebase. The animals were injected intraperitoneally (i.p.) with an equal

volume of 0.8 cc with 0.9 % saline. There are no universally recognized MPD dosage guidelines or blood levels to achieve optimum treatment. A study of 289 patients treated with MPD (White and Yadao 2000) reported that the range of doses was from 0.06 to 29.3 mg/kg with the majority being 1.0–3.0 mg/kg (Crutchley and Temlett 1999, Kollins et al. 2001, Solanto 1998 and Solanto 2000). Drug effects in rodents often require higher doses than in humans because they metabolize MPD more rapidly than humans (Gatley et al. 1999). Doses between 0.5 and 3.5 mg/kg MPD given intraperitoneally in rodents were reported to promote plasma peak concentration within the typical clinical range (Kuczenski and Segal 2002). The range of 5–10 mg/kg MPD is considered moderate dosage and above 10 mg/kg as a high dosage (Bowman and Kuhn 1996; Brandon and Steiner 2003; Kollins et al. 2001; Solanto 1998; Solanto 2000). The three treatment dosages 0.6, 2.5, and 10.0 mg/kg of MPD-D chosen in this study were based on our previous dose–response studies. Chronic treatment with 2.5 mg/kg and, in a few cases, also the 0.6 mg/kg MPD dose elicited behavioral sensitization (Gaytan et al. 1996, 1997, 2000a, 2000; Lee et al. 2008; Wanchoo et al. 2009; Yang et al. 2000a, 2001, 2000b, 2003, 2006a, 2006b, 2007). The doses in the present study correlate to low, medium, and high doses, respectively (Dafny and Yang 2006). Injections were made between 0630 and 0700 hours each day according to protocol (Table 1).

Procedure

Locomotor activity was recorded non-stop for 11 days using the CAAM system except during animal handling. The horizontal activity (HA), which measures the overall motor activity in the lowest sensor, was evaluated in this present study. The experiment was carried out in accordance with the guidelines of the NIH and the Declaration of Helsinki, and approved by our local animal welfare committee.

Data analysis

Data analysis was performed to assess dose–response effects of three different doses of MPD on the hourly total HA counts for EDs 1, 2, 7, 8, and 11 (Table 2). In addition to the three dosage groups, a control group was also used to ensure uniformity throughout the experiment (Table 1). The effect of MPD was divided into four phases of drug activity (Podet et al. 2010; Yang et al. 2006a, b, 2011). The four phases are: (1) Acute phase—the effect after MPD injection on ED 2 to ED 1, the baseline post-saline injection, was compared to observe whether a single (acute) injection was able to change the locomotor diurnal rhythm activity pattern. (2) Induction phase—the activity pattern on ED 7, the last day of the drug maintenance treatment, was compared to that of ED 2 to observe whether 6 days of MPD treatment induced any changes in activity pattern. (3) Washout phase (also known as withdrawal phase)—the activity patterns of ED 8, 9, and 10 were compared to that of ED 1 to observe whether the 6 days of MPD treatment (ED 2–7) altered the baseline activity levels of days without treatment (ED 8–10). (4) Expression phase—the activity pattern of ED 11 was compared to that of ED 1 to observe whether the effect of chronic MPD exposure during ED 2–7 was expressed after 3 days without treatment (ED 8–10).

Two forms of data analysis were performed to evaluate the dose–response effects of the three MPD doses. The 10-min activity counts were summed to hourly histograms and their mean and standard deviation was calculated. The hourly histograms with their mean and standard deviation were used to evaluate visually any changes in circadian rhythm pattern compared to the control histogram. The second evaluation used the 10-min counts to calculate the 24-h rhythms for each of the four phases using the cosine curve statistical analysis (CCSA) test (Bingham et al. 1982). This test analyzed the data using three parameters: MESOR (average activity represented by the curve and its peak activity), amplitude (distance from the MESOR to the

Table 1 Experimental protocol

	Control ($n = 8$)	0.6 mg/kg MPD ($n = 8$)	2.5 mg/kg MPD ($n = 8$)	10.0 mg/kg MPD ($n = 8$)
ED 1	Saline	Saline	Saline	Saline
ED 2–7	Saline	0.6 mg/kg MPD	2.5 mg/kg MPD	10.0 mg/kg MPD
ED 8–10	No injection	No injection	No injection	No injection
ED 11	Saline	0.6 mg/kg MPD	2.5 mg/kg MPD	10.0 mg/kg MPD

All four group rats received saline injection on ED 1. On EDs 2–7, each group received saline, 0.6, 2.5, or 10.0 mg/kg MPD injections, respectively. EDs 8–10 were washout days. On ED 11, each group was rechallenged with the same injection as during ED 2. The MPD challenge dose groups were injected at approximately 0700 hours

ED experimental day, *MPD* methylphenidate

Table 2 Statistical data of the experimental groups

	MPD dose	ED	MESOR	Amplitude	Acrophase
Acute phase (ED 2 vs 1)	0.6 mg/kg	1	342.51	192.33	15.67
		2	337.50	153.01	16.30
		p value	0.822	0.366	0.474
		F stat	0.051	0.821	0.515
	2.5 mg/kg	1	358.06	207.58	15.64
		2	366.57	220.33	16.16
		p value	0.778	0.783	0.480
		F stat	0.079	0.076	0.501
	10.0 mg/kg	1	366.37	153.97	17.72
		2	358.61	171.22	15.14
		p value	0.732	0.721	0.013
		F stat	0.117	0.128	6.223
Induction phase (ED 7 vs 2)	0.6 mg/kg	2	337.50	153.01	16.30
		7	354.34	200.80	15.52
		p value	0.540	0.274	0.339
		F stat	0.377	1.202	0.919
	2.5 mg/kg	2	366.57	220.33	16.16
		7	384.53	248.98	248.98
		p value	0.622	0.621	0.073
		F stat	0.244	0.245	3.24
	10.0 mg/kg	2	358.61	171.22	15.14
		7	303.11	201.85	14.47
		p value	0.114	0.582	0.485
		F stat	2.519	0.303	0.49
Washout phase (ED 8 vs 1)	0.6 mg/kg	1	342.51	192.33	15.67
		8	378.40	195.11	195.11
		p value	0.222	0.951	0.520
		F stat	1.499	0.004	0.416
	2.5 mg/kg	1	358.06	207.58	15.64
		8	392.07	235.30	15.74
		p value	0.311	0.587	0.898
		F stat	1.032	0.296	0.016
	10.0 mg/kg	1	366.37	153.97	17.72
		8	338.16	186.82	15.27
		p value	0.306	0.455	0.007
		F stat	1.052	0.56	7.317
Expression phase (ED 11 vs 2)	0.6 mg/kg	2	337.50	153.01	16.30
		11	376.15	242.88	16.56
		p value	0.162	0.041	0.730
		F stat	1.966	4.207	0.119
	2.5 mg/kg	2	366.57	220.33	16.16
		11	443.20	320.65	15.27
		p value	0.027	0.067	0.193
		F stat	4.979	3.377	1.706
	10.0 mg/kg	2	358.61	171.22	15.14
		11	334.97	174.22	14.74
		p value	0.497	0.957	0.697
		F stat	0.463	0.003	0.152

MESOR, amplitude and acrophase of EDs 1, 2, 7, 8, 11 and statistical analysis of the acute phase (ED 2 vs 1), the induction phase (ED 7 vs 2), the washout phase (ED 8 vs 10), and the expression phase (ED 11 vs 2) are shown

highest point of the approximating curve), and acrophase (time at which the maximum/amplitude occurs). The estimate of these three parameters provides the ability to test for statistically significant changes in HA pattern with regard to time and intensity within the 24-h experimental period. It is this parameterization that allows for accurate representation to find out whether a significant shift in HA circadian rhythm activity pattern occurred in the acute, induction, washout, or expression phases.

Results

Control (saline injection)

The locomotor activity of eight adult female WKY rats injected i.p., with 0.8 cc 0.9 % saline served as the control group. Each animal was injected every day between 0630 and 0700 hours for seven consecutive days and then a period of 3 days with no injection, followed by another saline rechallenge injection on ED 11 (Table 1). Recording of motor activity began after the first injection at about 0700 hours, nonstop until 24 h after the last injection of ED 11. Figure 1a shows a summary of hourly HA counts for ED 1, 2, 7, 8, and 11 of the saline control group, which shows the (control) rhythmic activity of a nocturnal animal: an increase in locomotor activity during the dark phase (night) and decreased motor activity during the light period (day). During ED 1, 2, 7, 8, and 11, the HA followed this general pattern with minor changes that were deemed insignificant (Fig. 1a). Figure 1b provides the superimposed 10-min counts of HA and the calculated CCSA test of all four groups on ED 1 post-injection, demonstrating that all the locomotor activity exhibits the same general locomotor activity pattern with only minor insignificant fluctuations, i.e., all animal groups have similar baseline activity pattern. Based on these findings, one can conclude that significant deviations from the locomotor activity obtained on ED 1 could be attributed to the drug (MPD) effect (Algahim et al. 2009; Lee et al. 2011; Bergheim et al. 2012). Due to the observation that HA obtained at ED 1 was the same as all other EDs in the control group and that all four groups had similar activity pattern post-injection on ED1, it follows that the activity of ED 1 after saline injection in each MPD group can and was used as the control for the drug effect of that dose group.

MPD acute effects (comparing ED 2 to ED 1)

The 0.6 mg/kg MPD dose showed an initial increase in activity on ED 2 following MPD injection compared to ED 1 (Fig. 2a—0.6 mg/kg dose) and return to baseline level for the remaining period. The CCSA showed no significant alteration in the HA pattern activity on ED 2 compared to ED 1 (Fig. 2b—0.6 mg/kg; Table 2). The 2.5 mg/kg MPD injection caused an increase in activity during the initial

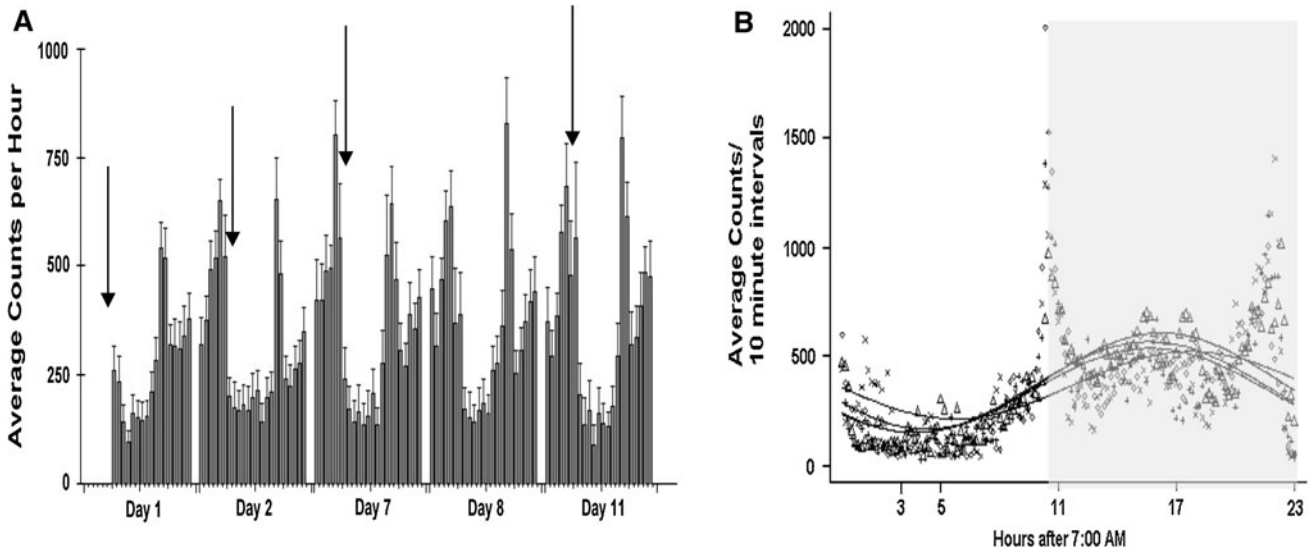

Fig. 1 Baseline activity pattern. **a** Hourly histogram of the control group demonstrating consistent rhythm of the average horizontal activity counts per hour of EDs 1, 2, 7, 8, and 11. The *arrows* indicate time of injection (saline) and *shaded areas* indicate the dark period of the 23-h experimental period. Only experimental day 1 begins at 0600 hours, whereas all other days thereafter begin at 0000 hours. The rhythmic activity of a nocturnal animal, i.e., increased locomotor activity during the dark phase (night) and decreased motor activity during the light period (day), is observed. **b** A 24-h cosine curve statistical analysis of horizontal activity circadian rhythm pattern in counts per 10 min, post-injection, for all treatment groups on ED 1. The locomotor activities of the four animal groups exhibit the same general locomotor activity pattern with only minor insignificant fluctuations. Time 0 = 0700 hours; the shaded area indicates a dark period of the 24-h experimental period. *CCSA* cosine curve statistical analysis

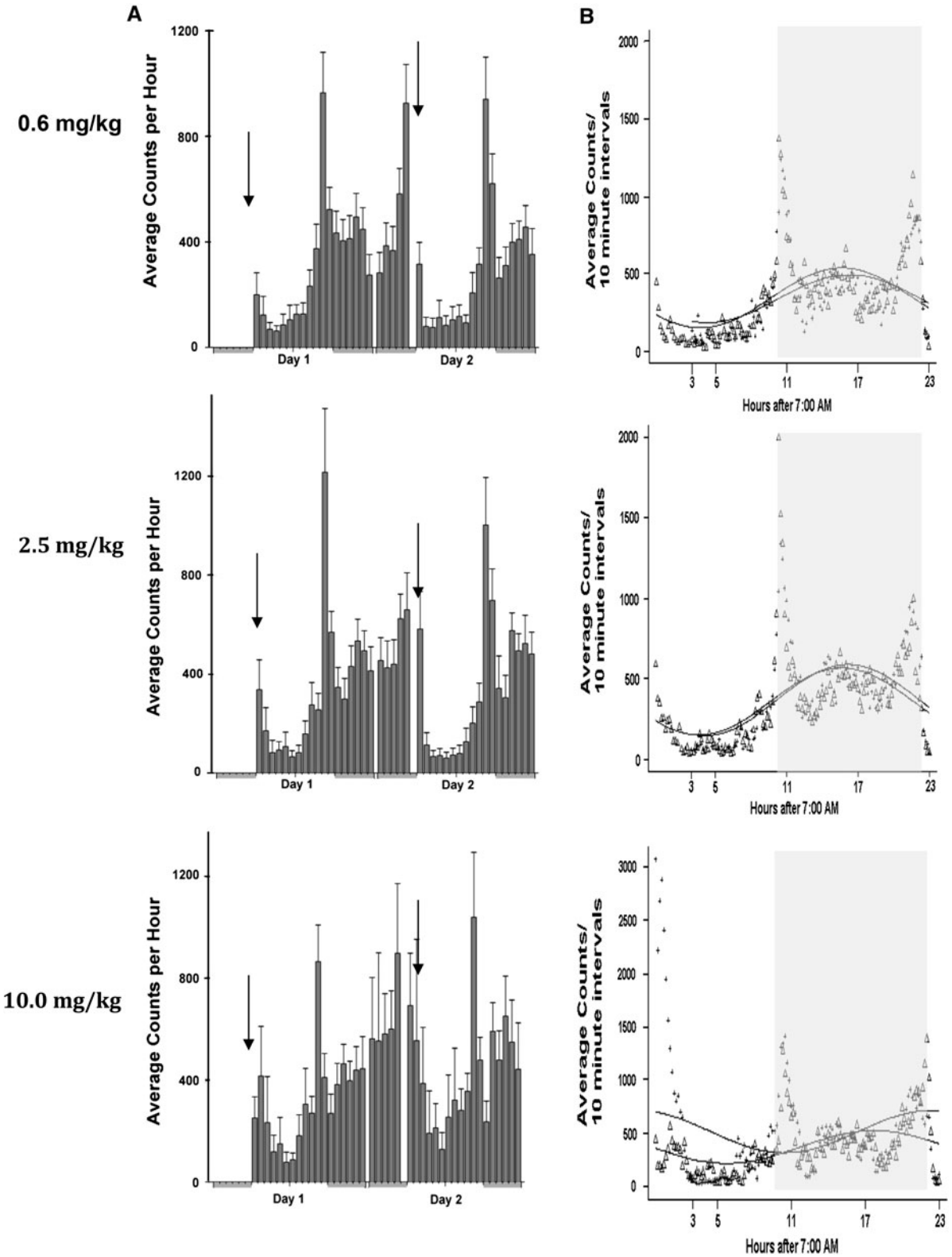

Fig. 2 Acute phase response in the three experimental dose groups. **a** Histogram representation of HA counts/h of experimental days 1 and 2. *Arrow* indicates time of injection (saline on ED1 and MPD on ED2). **b** Cosine curve comparing experimental days 1 and 2 over a 23-h period post-drug injection. Time 0 = 0700 hours; the shaded area indicates a dark period of the 24-h experimental period. The CCSA test shows no significant alteration in the HA pattern activity on ED 2 compared to ED 1 for the 0.6 and 2.5 mg/kg dose groups; the 10.0 mg/kg dose group exhibited a statistical significant decrease in acrophase

post-injection hours and between 1800 and 2000, i.e., from the 11th to 13th hour post-injection (Fig. 2a—2.5 mg/kg). However, the CCSA test (Fig. 2b—2.5 mg/kg) found this increase in activity at ED 2 compared to ED 1 to be of no statistical significance. The acute 10 mg/kg MPD dose exposure resulted in an increase in HA within the first 3 h post-injection (Fig. 2a, b—10 mg/kg). This immediate high-activity response to MPD injection exerted an exaggerated effect on the 24-h fitted CCSA test, i.e., "pulling" the curve "up" at the far left at approximately hour zero (Fig. 2b—10 mg/kg). To appropriately parameterize the long-term effects of MPD on the locomotor activity patterns, these first 3 h of data were excluded from the CCSA test, resulting in a cosine curve more accurately representing the long-term effects of the entire time post-injection pattern of ED 2. These data were used for the analysis of this paper. The 10 mg/kg MPD dose also exhibited an increase in activity between 6th and 8th, 9th and 12th, and 13th and 16th hours post-injection (Fig. 2a—10 mg/kg). The CCSA showed statistically significant decrease in the acrophase ($p = 0.013$) (Fig. 2c—10 mg/kg; Table 2).

MPD induction phase (comparing ED 7 to ED 2)

The 0.6 mg/kg MPD injection at ED 7 elicited the same increase in activity post-MPD injection as at ED 2 (Fig. 3a—0.6 mg/kg). However, this increase in activity was prolonged and lasted from 0 to 5th hour post-injection. The activity also increased during the 7th–10th and 11th–16th hours after injection on ED 2 (Fig. 3a—0.6 mg/kg dose). The statistical comparison using the CCSA test (Fig. 3b—0.6 mg/kg; Table 2) showed that these changes in locomotion were not statistically different (Table 2). The locomotor activity following 2.5 mg/kg MPD at ED 7 exhibited an increase in activity that lasted from 0 to 11th hour after injection. In addition, an increase in activity was seen again from 13th to 16th hour after injection (Fig. 3a—2.5 mg/kg dose). However, the CCSA test showed that these changes in locomotive activity pattern were statistically insignificant (Fig. 3b—2.5 mg/kg; Table 2), i.e., 6 days of 2.5 mg/kg MPD had no effects on the HA circadian activity patterns. The 10 mg/kg of MPD exposure on ED 7 compared to ED 2 locomotor activity only exhibited an increase in activity between the 1st and 5th hour after injection (Fig. 3a—10 mg/kg). The CCSA test for this group shows the change to be statistically insignificant (Fig. 3b—10 mg/kg; Table 2).

Washout phase (comparing ED 8 to ED 1)

On ED 8, MPD injections were held to determine whether withdrawal was induced by the six daily administrations of MPD. The 0.6 mg/kg MPD dose group exhibited increased activity from 0 to 2nd hour post-injection, at the 5th hour, and 10–12th hour post-injection (Fig. 4a—0.6 mg/kg). The CCSA test of ED 8 versus ED 1 locomotor activity was found to be statistically insignificant (Fig. 4b—0.6 mg/kg; Table 2). The 2.5 mg/kg MPD dose group exhibited an increase in activity from 0 to 2nd, 5th to 7th, 9th to 12th, and 13th to 17th hours post-injection (Fig. 4a—2.5 mg/kg dose curve). However, the CCSA test shows these increases to be statistically insignificant (Fig. 4b—2.5 mg/kg; Table 2). The 10 mg/kg MPD dose group also exhibited an increase in locomotor activity from 0 to 4th and 9th to 17th hours post-injection (Fig. 4a—10 mg/kg). The CCSA test showed statistical significance with regard to the acrophase ($p = 0.007$) (Fig. 4b—10 mg/kg; Table 2). At the beginning of ED 8, all of the experimental animals showed an increase in activity at the time that they had received the MPD injections during the previous 6 days. This suggests that the animals were expecting to get the next dose of the MPD drug or that they were expressing behavioral withdrawal.

MPD expression phase (comparing ED 11 to ED 2)

To determine whether the changes induced by repetitive MPD administration were transient or long-lasting, the locomotor activity of ED 11 was compared to that of ED 2. The 0.6 mg/kg MPD groups exhibited an increase in activity of during the 3rd and 12th–17th hours post-MPD injection (Fig. 5a—0.6 mg/kg). The CCSA test shows a significant increase in amplitude ($p = 0.041$) (Fig. 5b—0.6 mg/kg; Table 2). The 2.5 mg/kg MPD groups exhibited an increase in activity from 0 to 5th hour post-injection, followed by an increase in activity between 8th and 12th hour post-injection, as well as 13th to 17th hour post-injection (Fig. 5a—2.5 mg/kg dose). The CCSA test of the ED 11 activity compared to that of ED 2 activity post-MPD exposure exhibits significant difference in the MESOR ($p = 0.027$) (Fig. 5b; Table 2—2.5 mg/kg). The 10 mg/kg MPD group at ED 11, i.e., after six daily MPD exposures and three washout days, showed an initial increase in locomotor activity when compared with ED 2 between the 0 and 4th hour post-injection followed by an increase in activity from 11th to 13th hour post-injection (Fig. 5a—10.0 mg/kg dose histogram). The CCSA test shows statistically insignificant difference between ED 11 and ED 2 (Fig. 5b—10 mg/kg cosine curve; Table 2).

Discussion

The neurotransmitter dopamine facilitates multiple critical facets of human physiology such as locomotion, cognition,

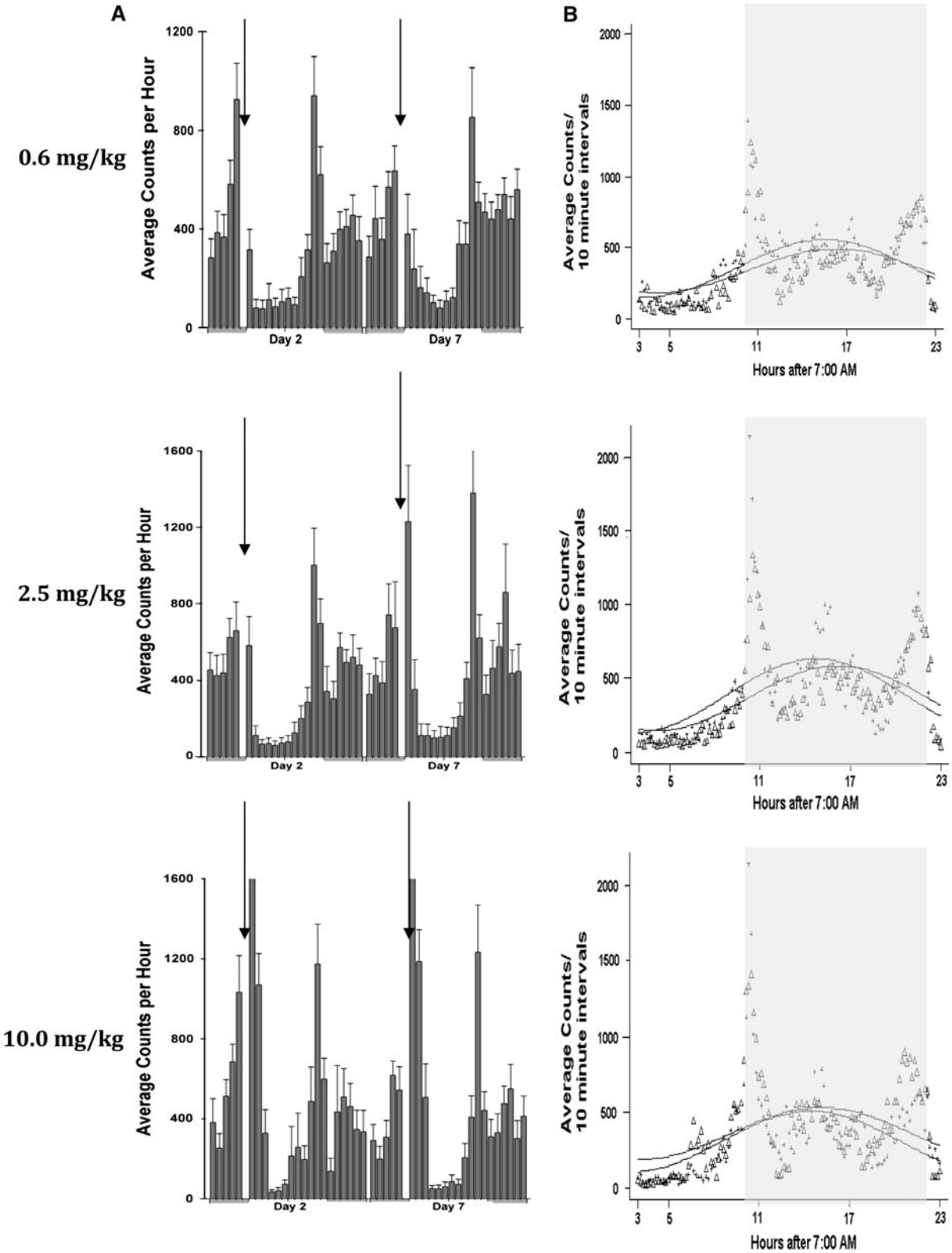

Fig. 3 Induction phase effect in the three experimental dose groups. **a** A histogram representing HA counts/h of experimental days 2 and 7. *Arrows* indicate time of injection (MPD). **b** Cosine curve comparing experimental days 2 and 7 over a 23-h period post-drug injection. Time 0 = 0700 hours; the *shaded area* indicates a dark period of the 24-h experimental period. The CCSA test shows no significant alteration in the HA pattern activity for all three dose groups

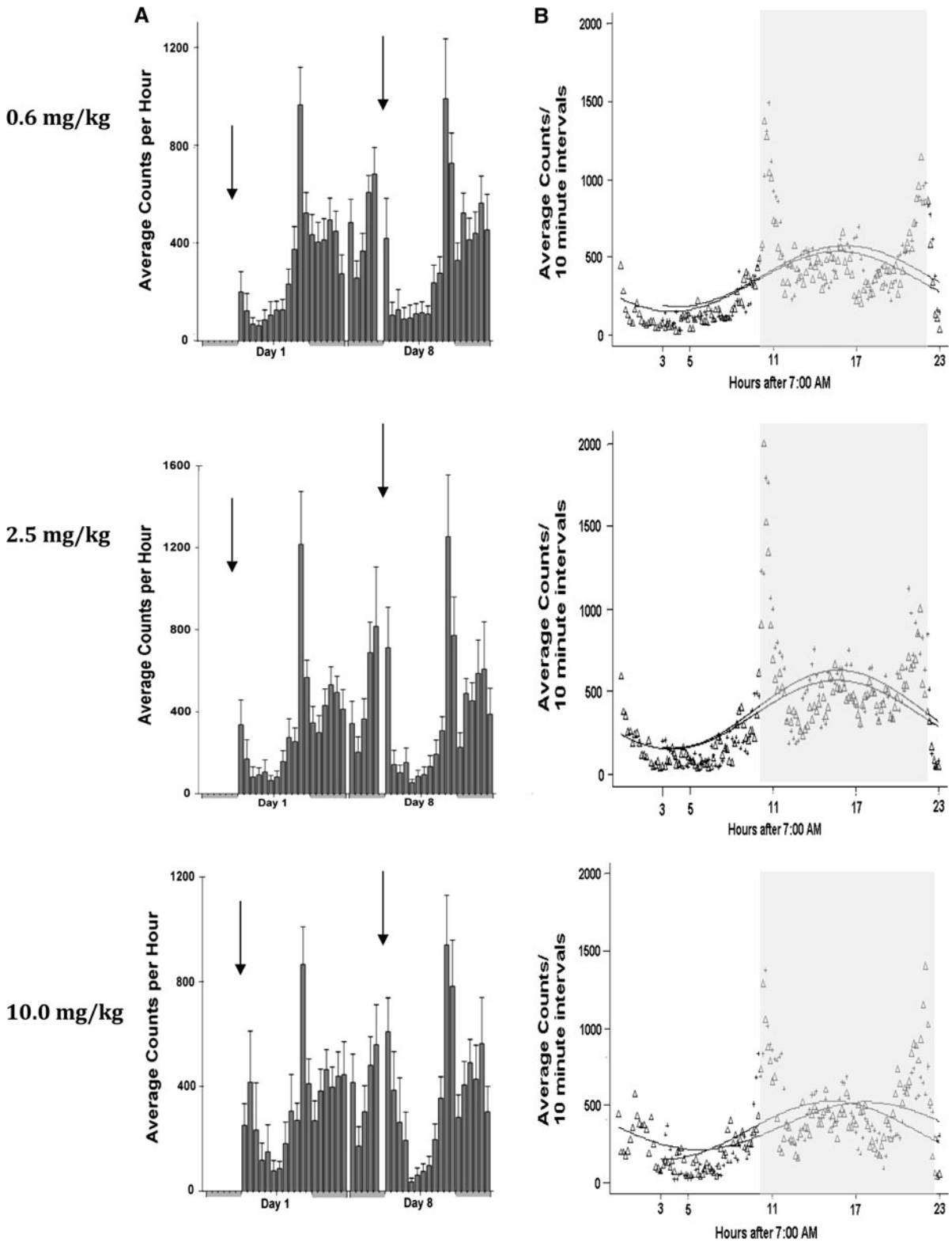

Fig. 4 Washout phase effect in the three experimental dose groups. **a** Histogram representation of HA counts/h of experimental days 1 and 8. *Arrow* indicates time of injection (saline on experimental day 1). At the beginning of ED 8, all of the experimental animals showed an increase in activity at the time that they had received the MPD injections during the previous 6 days. **b** Cosine curve comparing experimental days 1 and 8 over a 23-h period. Time 0 = 0700 hours; the *shaded area* indicates a dark period of the 24-h experimental period. The CCSA test showed statistical significance with regard to the acrophase of the 10.0 mg/kg MPD dose group

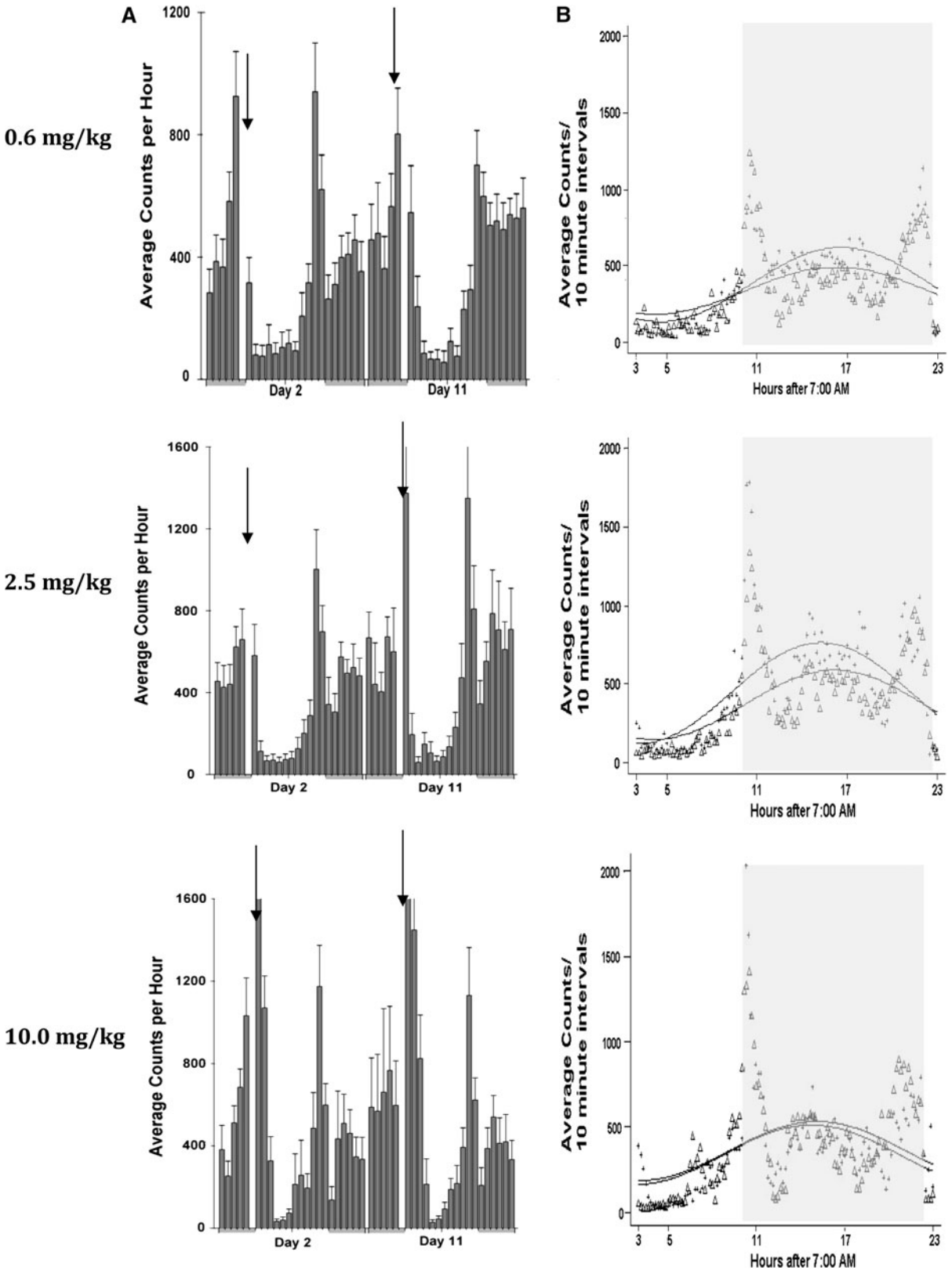

Fig. 5 Expression phase effect in the three experimental dose groups. **a** Histogram representation of HA counts/h of experimental days 2 and 11. *Arrows* indicate the time of injection (MPD). **b** Cosine curve comparing experimental days 2 and 11 over a 23-h experimental period. Time 0 = 0700 hours; the *shaded area* indicates a dark period of the 24-h experimental period. The CCSA test shows statistical significance in amplitude of the 0.6 mg/kg MPD group and MESOR of the 2.5 mg/kg MPD group

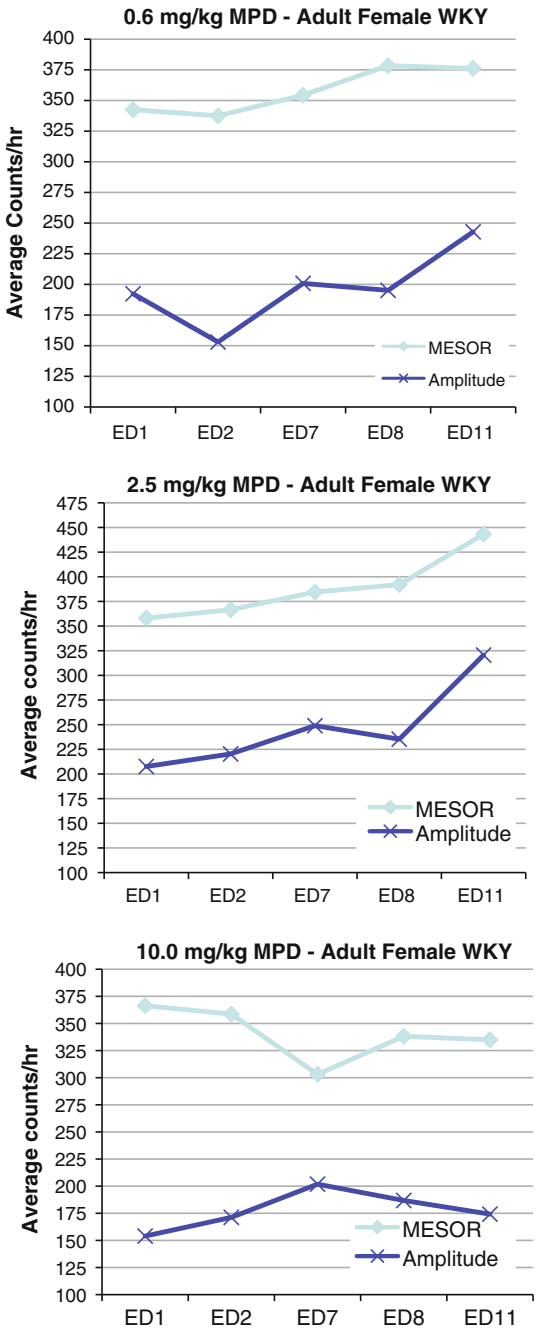

Fig. 6 MESOR and amplitude of the three experimental dose groups throughout the experimental days

emotion, and reward. Thus, it is prudent that a pharmacological agent that increases the extracellular concentrations of dopamine in synaptic clefts be further investigated, especially when the prescribed and non-prescribed usage of such agent is on the rise. It would also stand to reason that animal models of a known subpopulation that use this substance be specifically studied, since using human subjects for this purpose in a prospective manner would be impractical and unethical.

Three major findings of this study

(1) The 0.6 mg/kg dose group shows an increased amplitude at ED 11, the expression phase, that was statistically significant ($p = 0.041$) (Table 2). This change in locomotor activity after a washout period implied that chronic 0.6 mg/kg MPD exposure altered the circadian rhythm locomotor activity pattern of the animals and/or that the animals were sensitized to 0.6 mg/kg MPD. (2) The 2.5 mg/kg dose group demonstrated MESOR trending up over the 11 EDs and statistical significance ($p = 0.041$) at the expression phase (Table 2; Fig. 6). The chronic exposure of 2.5 mg/kg MPD was able to establish a new baseline locomotor activity pattern. This is in contrast to the MESOR of the 0.6 mg/kg dose group, which also trended up, but the p value did not reach statistical significance (Table 2; Fig. 6). Perhaps, the 0.6 mg/kg MPD dose was too low and not enough MPD and, subsequently, DA accumulated in the synaptic clefts to effect a change in locomotor activity as in the 2.5 mg/kg dose group. Perhaps, more time is needed for this change in locomotor activity to manifest as statistical significance. Of note, comparing the change in amplitude of the 2.5 mg/kg dose group from ED8 to ED11 (235 → 320 average counts/10 min) to the change in amplitude from ED2 to ED7 (220 → 248 average counts/10 min), it was observed that the change in amplitude was four times greater at the expression phase than the induction phase (Table 2; Fig. 6). One could not help but wonder that perhaps a degree of sensitization was at play. (3) The 10 mg/kg dose group showed that the acrophase shifted approximately 2.5 h earlier on ED 2 ($p = 0.013$) (Table 2). This change in locomotor activity pattern was effected by a single 10.0 mg/kg MPD injection and persisted through six daily injections, 3 days of washout, and upon MPD rechallenge at ED 11, suggesting that, indeed, a new baseline of locomotor activity had been established. The change in acrophase also highlights the fact that it is important to analyze the data and trends fully, despite the numerical analysis suggesting statistical insignificance, i.e., acrophase of ED 11 versus 2 was $p = 0.697$, while the acrophase was actually shifted ~2.5 h earlier from EDs 2 to 11. While the change in the amplitude of circadian rhythm activity pattern from ED 11 versus 2 did not show a statistical significance, it may be due to the expression of tolerance, i.e., the 10 mg/kg MPD dose did not alter the activity pattern but induced tolerance, which is also a long-term effect of the drug.

Psychostimulants affecting neuroadaptation

Neuroadaptation by mesocorticolimbic dopaminergic pathway which includes the ventral tegmental area (VTA), nucleus accumbens (NAc), and the prefrontal cortex (PFC)

is a major factor in the development of behavioral sensitization (Chen et al. 2009; Chong et al. 2012; Claussen and Dafny 2012; Everitt and Robbins 2005; Kalivas and Stewart 1991; Nestler 2001; Podet et al. 2010; Robinson and Becker 1986; Salek et al. 2012). Neuroadaptation is mediated by neuronal structural plasticity manifested by changes in the size of cell bodies or changes in spine morphology, such as arborization and the density of dendritic spines (Robinson and Kolb 2004; Russo et al. 2010; Sklair-Tavron et al. 1996). Chronic psychostimulant exposure leads to an increased density and complexity of spines of medium-sized spiny neurons in the NAc (Lee et al. 2006), which result in long-term potentiation (Nagerl et al. 2004; Okamoto et al. 2004; Matsuzaki et al. 2004). MPD initially interacts with dopamine and glutamine in the dendritic spines of medium-spiny neurons (MSN) in the ventral and dorsal striatum (Robinson and Kolb 2004). This study shows that the 0.6 mg/kg MPD dose failed to elicit effect following the initial MPD exposure, while eliciting increased locomotor activity amplitude only after repetitive MPD exposure at the expression phase. Perhaps, silent receptors were recruited (Boudreau et al. 2007; Boudreau and Wolf 2005; Conrad et al. 2008; Huang et al. 2009; Malenka and Nicoll 1999; Marie et al. 2005) following repetitive exposure to the drug, and the behavioral response manifested as increased amplitude.

Different brain region exhibit different levels of DA receptor types (Wirz-Justice 1987). Both D1 and D2 receptors are found in high concentration in NAc (Girault and Greengard 2004) with excitatory and inhibitory roles, respectively (Einhorn et al. 1988; Ruskin et al. 2001; Shi et al. 1997). D1-like DA receptors mediate extracellular signal-kinase (ERK) which upregulates ΔFosB, a marker of increased sensitivity to behavioral effects and increased motivation for the drug (Nestler 2001; Nestler and Malenka 2004), which is reported to induce long-term neuroadaptations in the brain (Shi and Mcginty 2010; Zhang et al. 2004). When D1 receptors are inhibited, there is an increase in phosphorylation of cAMP response element-binding protein (CREB) which leads to homeostatic negative feedback adaptation, inhibiting sensitivity, i.e., behavioral tolerance (Chao and Nestler 2004; Nestler and Malenka 2004). On the other hand, D2-like DA receptors are reported to exert an inhibitory effect (Ferguson et al. 2010; Kreitzer and Malenka 2008; Zhang et al. 2004). Of note, in this experiment, the 10.0 mg/kg MPD dose group showed MESOR trending down during the acute phase (366.37 → 358.61 average counts/10 min), further down during induction (358.61 → 303.11 average counts/10 min), up during washout (303.11 → 338.16 average counts/10 min), and, finally, down during the expression phase (338.16 → 334.97 average counts/10 min). This trend suggests that chronic exposure of 10.0 mg/kg MPD exerts an attenuation effect on the animals' locomotor activity. Perhaps at this dosage, D2 receptors were preferentially activated. Furthermore, the magnitude of decrease in MESOR during the expression phase was less than during the induction phase, and behavior tolerance may be the underlying reason for this observation. Since chronic treatment of MPD showed an increase in locomotion, one might assume that psychostimulants not only inhibit uptake of DA by blocking the DAT, but also may increase production of D1 and/or D2 receptors (Kleven et al. 1990).

The chronic MPD effects observed in this study suggest that MPD, like cocaine, is capable of inducing both tolerance and sensitization (Izenwasser and French 2002). Sensitization was observed in this study at 0.6 and 2.5 mg/kg MPD, while tolerance was observed at 10.0 mg/kg MPD. Cocaine and amphetamine may not only inhibit uptake of DA, but also induce the production of D1 and D2 receptors (Kleven et al. 1990). Therein, the question arises as to whether chronic administration of MPD would also induce both D1 and D2 receptors, which may account for the simultaneous manifestation of opposing behavioral responses, sensitization, and tolerance.

Conclusion

After chronic treatment of MPD and a washout period, all three dose groups manifested changes in diurnal locomotor activity indices upon rechallenge with the drug. These changes in locomotor activity pattern are interpreted as long-term effect exerted by MPD. Perhaps, the behavioral changes resulted from alteration of the clock genes, regulation of transcription factors, or preferential activation of receptors. Further investigation into the mechanism of change in the circadian rhythm pattern exerted by MPD, thereby affecting the various homeostatic functions within the body, is warranted.

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