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Research report

MDMA alters the response of the circadian clock to a photic and non-photic stimulus

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Abstract

3,4-Methylenedioxymethamphetamine (MDMA or 'Ecstasy') is a widely used recreational drug that damages serotonin 5-HT neurons in animals and possibly humans. Published literature has shown that the serotonergic system is involved in photic and non-photic phase shifting of the circadian clock, which is located in the suprachiasmatic nuclei. Despite the dense innervation of the circadian system by 5-HT and the known selective neurotoxicity of MDMA, little is known about the effects of MDMA on the circadian oscillator. This study investigated whether repeated exposure to the serotonin neurotoxin MDMA alters the behavioural response of the Syrian hamster to phase shift to the serotonin 5-HT1A/7 receptor agonist 8-hydroxy-2-(di-*n*-propylamino) tetralin hydrobromide (8-OH-DPAT). This agonist was administered under an Aschoff Type I (CT8) and Aschoff Type II (ZT8) paradigm (5 mg/kg) and was given before and after treatment with MDMA (10, 15 and 20 mg/kg administered on successive days). Pre-treatment with MDMA significantly attenuated phase shifts to 8-OH-DPAT. We also tested the ability of the clock to phase shift to a photic stimulus after treatment with MDMA. A 15-min light pulse (mean lux 125 at CT14 or ZT14) was administered before and after treatment with MDMA. Phase shifts to a photic stimulus were significantly attenuated by pre-treatment with MDMA. Our study demonstrates that repeated exposure to MDMA may alter the ability of the circadian clock to phase shift to a photic and non-photic stimulus in the hamster. Disruption of circadian function has been linked with a variety of clinical conditions such as sleep disorders, mood, concentration difficulties and depression, consequently outlining the potential dangers of long-term ecstasy use.

Theme: Neural basis of behavior

Topic: Biological rhythms and sleep

Keywords: Circadian; 3,4-Methylenedioxymethamphetamine; Serotonin; Suprachiasmatic nucleus; Photic and non-photic

1. Introduction

The suprachiasmatic nuclei (SCN) of the hypothalamus serve as the primary circadian pacemaker in mammals [18]. Light is the principal cue responsible for the synchronisation of the pacemaker to daily environmental rhythms [33]. However, non-photic behavioural events, such as exercise and social stimuli also alter the circadian phase in mammals [26,22].

Photic information necessary for the resetting of the circadian pacemaker is conveyed directly to the clock from the retina via the retinohypothalamic tract [17]. A second indirect pathway conveys photic and non-photic information to the clock from the geniculohypothalamic tract via a projection from the intergeniculate leaflet [29,5,16]. The third major source of input to the SCN arises from a dense serotonergic innervation originating from the midbrain raphe [2,25], and is thought to be involved in non-photic phase shifting of the clock.

Serotonin (5-HT) is a neurotransmitter involved in a variety of physiological and behavioural processes. A convergence of evidence supports the involvement of the serotonergic system in the regulation of the circadian pacemaker [19,20]. The serotonin 5-HT1A/7 receptor agonist 8-hydroxy-2-(di-*n*-propylamino) tetralin hydro-

Abbreviations: MDMA, 3,4-Methylenedioxymethamphetamine; 5-HT, serotonin; SCN, suprachiasmatic; ZT, zeitgeber time

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bromide (8-OH-DPAT) has chronobiological effects on the circadian system. Systemic application of 8-OH-DPAT to hamsters housed in constant darkness (DD) induces phase shifts consistent with the non-photic phase response curve [11,37]. Although the phase shifting effect of some drugs may be due to elevated activity or arousal, 8-OH-DPAT has a direct effect on the circadian clock [8]. This serotonin agonist may alter the circadian behaviour of the hamster by acting at the level of the raphe [21], although other studies suggest that 8-OH-DPAT may act at the level of the SCN [10]. In addition, electrical recordings from the SCN in vitro demonstrate that 8-OH-DPAT can reset the phase of the clock directly by inducing large phase shifts when applied during the subjective day [38,30,7]. Finally, neurotoxic lesions of the 5-HT projection from the median raphe to the SCN modulate activity phase onset [20].

A substantial body of evidence demonstrates that 5-HT can modify the response of the circadian clock to light. Electrical stimulation of the midbrain raphe blocks phase advances to light in the hamster [33]. Recently, it was shown that the selective 5-HT1A receptor antagonist WAY 100635 augments phase shifts to light [39]. Also systemic administration of the 5-HT1A/7 receptor agonist 8-OH-DPAT dose dependently attenuates light-induced phase shifts in free running hamsters [32]. These inhibitory actions of 8-OH-DPAT on phase shifts to light may occur at the level of the SCN [10,41]. In addition it has been shown that 8-OH-DPAT inhibits field potentials recorded in response to optic nerve stimulation [32]. Alternatively decreasing serotonergic input augments phase shifts to light. The serotonin neurotoxin 5,7-dihydroxytryptamine increased photic phase shifts in hamsters [24]. Similarly, lesions of 5-HT fibres in the SCN increased light-induced phase delays of the free running rhythm in mice [9].

The synthetic amphetamine derivative 3,4-Methlyenedioxymethamphatamine (MDMA) is a recreational drug of abuse. Accumulating evidence has documented that MDMA is a selective serotonergic neurotoxin in rodents and non-human primates [40,3,28,34]. Despite the dense innervation of the circadian system by 5-HT and the known selective neurotoxicity of MDMA, little is known about the effects of MDMA on the circadian oscillator. The only known evidence suggests that MDMA may act by altering the 5-HT receptor activity at the level of the SCN [7]. Since 5-HT innervation from the raphe nuclei is involved in circadian clock function, and MDMA causes damage to 5-HT axon terminals in the brain, the present study aimed to investigate whether repeated exposure to MDMA alters the activity of the biological clock. Specifically, we tested the ability of the Syrian hamster to phase shift to the serotonin 5-HT1A/7 receptor agonist 8-OH-DPAT before and after treatment with MDMA. In addition we have investigated the ability of the circadian pacemaker to phase shift to a photic stimulus, following MDMA treatment.

2. Material and methods

2.1. Animals and housing

Male Syrian hamsters were purchased from Harlan Sprague–Dawley, Oxon, UK. Upon arrival in the laboratory, animals were placed in a light–dark cycle (LD 14:10), room temperature 22±2 °C. Animals were housed in individual polypropylene cages with nest boxes (13×9×8 cm) which contained a stainless running wheel (16 cm in diameter). When animals were housed in constant darkness (DD) the room was illuminated under constant dim red light using safelight lamps fitted with Kodak filter OA 152-149 (Eastman Kodak, Rochester, NY, USA).

2.2. Recording environment

Throughout the experiments, activity was recorded by wheel revolutions activating microswitches detected by Dataquest Pro-Data software (Data Sciences, Roseville, MN, USA). This was set to record and store the number of wheel revolutions into 10-min bins, continuously.

2.3. Data analysis

Activity onsets were defined as the first 10-min bin with at least 50 wheel revolutions followed by another bin with 50 or more revolutions within 30 min and following an activity-free rest period of greater than 6 h. Two phase shifting paradigms were used in this experiment.

2.3.1. Aschoff Type I design

Animals received a pulse whilst in constant darkness. Phase shifts were determined by calculating a regression line for the seven onsets before the manipulation and extrapolated to the day of the pulse. The three onsets including the pulse were omitted for possible transients. A second regression line was calculated from the fourth through tenth post pulse and projected back to the pulse day. The difference between the onsets projected from the pre and from the post pulse regression lines was taken as the phase shift.

2.3.2. Aschoff Type II design

Animals were maintained in a light–dark cycle (LD). On the day of the pulse, lights were turned off immediately after treatment. Animals remained in constant darkness for the next 10 days to assess free running rhythms. This design enables experimenters to administer stimuli to a large number of animals at the same clock time and zeitgeber time [8,27]. Phase shifts were determined by subtracting the onset time on the day before injection from a regression line calculated from the fourth through tenth post pulse projected back to the pulse day.

2.4. Aschoff Type I

2.4.1. Protocol

Fifteen animals (40 days old) were kept in a 14:10 LD cycle for 3 weeks before being transferred into constant conditions. After 7 days in DD, all animals were exposed to a 15-min light pulse (mean lux 125) beginning at CT14. Animals free ran for 10 days. Following this, all animals received intraperitoneal (i.p.) 8-OH-DPAT (Sigma, Poole, Dorset, UK) injections at CT8 (5 mg/kg). After 10 days in DD, the previous light–dark cycle was reinstated. Seven days into the LD, nine animals received the first of three subsequent injections of MDMA (gifted from the National Institute of Health NIH, USA). MDMA was administered in increasing doses, over three consecutive days (10, 15, 20 mg/kg) whilst six control animals received vehicle (saline) injections. MDMA and saline were administered during the subjective day. Wheel running activity was not recorded for 17–21 days around the MDMA dosing. Animals spent a further 10–14 days in LD before being transferred back to constant conditions. After 7 days in constant darkness all animals received the second injection of 8-OH-DPAT at CT8. After 11 days in DD, all animals were exposed to a light pulse at CT14. Animals were maintained in constant conditions for 10 days.

2.5. Aschoff Type II

2.5.1. Protocol

Thirteen animals (40 days old) were maintained in a 14:10 LD cycle for 3 weeks prior to the experiment. All animals were exposed to a 15-min light pulse (mean lux 125), beginning 2 h after lights off. This is a time when light induces phase delays in hamsters previously entrained to a 14:10 light–dark cycle. Lights were turned off at the end of the light pulse and remained off for a further 10 days. Animals were then re-entrained to the previous L/D cycle for 14 days. On the 15th day all animals received 8-OH-DPAT (5 mg/kg) injections 4 h before lights off. This is a time when DPAT induces phase advances of the circadian clock that previously was entrained to a 14:10 light–dark cycle. Lights were turned off immediately after injections and animals spent a further 10 days in DD. Animals were then re-entrained to a 14:10 LD. Nine days into the LD cycle animals received the first of three subsequent injections of MDMA (10, 15, 20 mg/kg) or vehicle injection during the subjective day. Animals remained in this LD cycle for a further 14 days. Wheel running was not recorded for 16 −19 days around the MDMA dosing. On the 15th day of LD, animals received the second injection of 8-OH-DPAT 4 h prior to lights off. Animals were then immediately placed in constant darkness for 10 days post pulse. Following this freerun, hamsters were re-entrained to a LD cycle for 14 days, before being exposed to the second light pulse 2 h after lights off. Lights were turned off immediately after the light pulse and remained off for a further 10 days.

3. Results

3.1. Aschoff Type I paradigm

A two-way ANOVA was used to compare phase shifts to the serotonin agonist 8-OH-DPAT before and after treatment with MDMA or vehicle (Fig. 1). This indicated a significant main effect of condition (MDMA or vehicle; $F_{(1,13)}=12.92$, $P<0.005$) and a significant main effect of time (pre and post; $F_{(1,13)}=27.70$, $P<0.001$). This was qualified by a significant condition versus time interaction ($F_{(1,13)}=22.88$, $P<0.001$). Hamsters phase shifted significantly less to the serotonin agonist 8-OH-DPAT after being dosed with MDMA (Tukey HSD, $P<0.001$). In addition, there were no significant differences between the two phase advances seen in response to DPAT in the animals not treated with MDMA, indicating that the time interval of over 4 weeks between agonist injections did not alter the response of the circadian system (Fig. 2).

There was also an effect on phase shifts to light as shown by a two-way ANOVA used to compare phase changes in response to light pulses prior to and after treatment with MDMA or vehicle (Fig. 3). There was a significant main effect of time (pre and post; $F_{(1,13)}=8.37$, $P<0.05$) and no significant main effect of condition. This was qualified by a significant condition versus time interaction ($F_{(1,13)}=20.27$, $P<0.001$). Hamsters phase shifted significantly less to the 15 min of light after being treated with MDMA (Tukey HSD, $P<0.05$).

3.2. Aschoff Type II paradigm

A two-way ANOVA was used to compare phase shifts to the serotonin agonist 8-OH-DPAT before and after treatment with MDMA or vehicle in animals dropped into constant conditions from a light–dark cycle (Fig. 1). This indicated a significant main effect of condition (MDMA or vehicle; $F_{(1,11)}=36.26$, $P<0.0001$), and a significant main effect of time (pre and post, $F_{(1,11)}=128.91$, $P<0.0001$). This was qualified by a significant condition versus time interaction ($F_{(1,11)}=105.26$, $P<0.0001$). Hamsters under this second paradigm also phase shifted significantly less to the serotonin agonist 8-OH-DPAT after being dosed with MDMA (Tukey HSD, $P<0.001$). In addition, there were no significant differences between the two phase advances seen in response to DPAT in the animals not treated with MDMA, indicating that the time interval of over 5 weeks between agonist injections did not alter the response of the circadian system (Fig. 4).

Finally, there was also an effect on phase shifts to light shown under this second paradigm (Fig. 3). A two-way

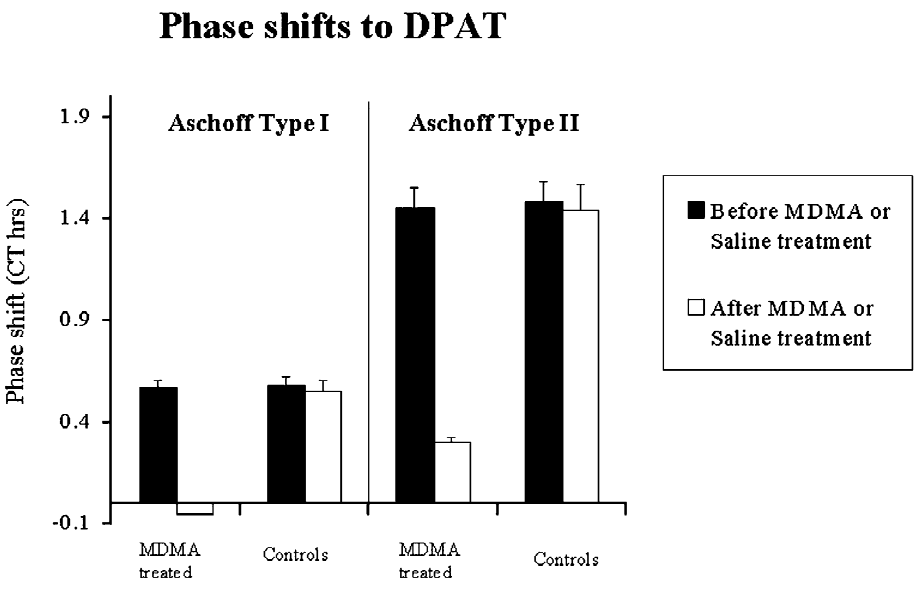

Fig. 1. A histogram depicting differences in mean phase shifts to 8-OH-DPAT before and after treatment with MDMA under an Aschoff Type I and II paradigm. Standard error of the means are included.

ANOVA compared phase changes in response to light pulses prior to and after treatment with MDMA or vehicle. There was a significant main effect of condition (MDMA or vehicle; $F_{(1,11)}=6.3$, $P<0.05$), and a significant main effect of time (pre and post, $F_{(1,11)}=10.25$, $P<0.01$). This was qualified by a significant condition versus time

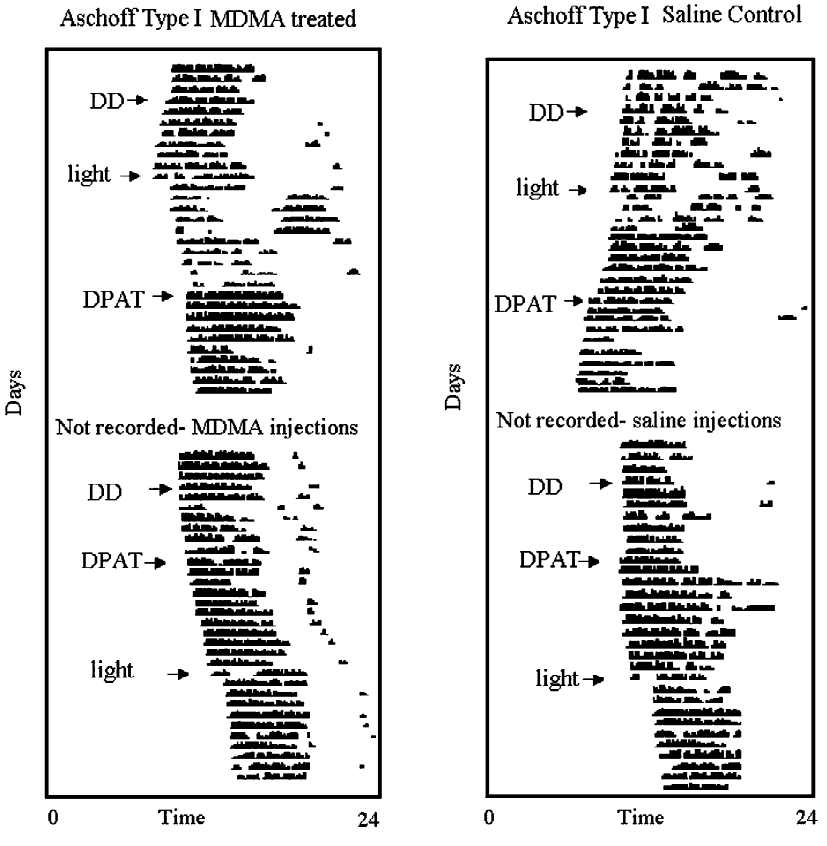

Fig. 2. Representative actograms illustrating phase shifts to 8-OH-DPAT at CT8 and light at CT14 before and after treatment with MDMA under an Aschoff Type I paradigm. The vertical of the actograms shows days as the experiment progressed and the horizontal represents the 24-h time period. The arrow denotes the day of the pulse.

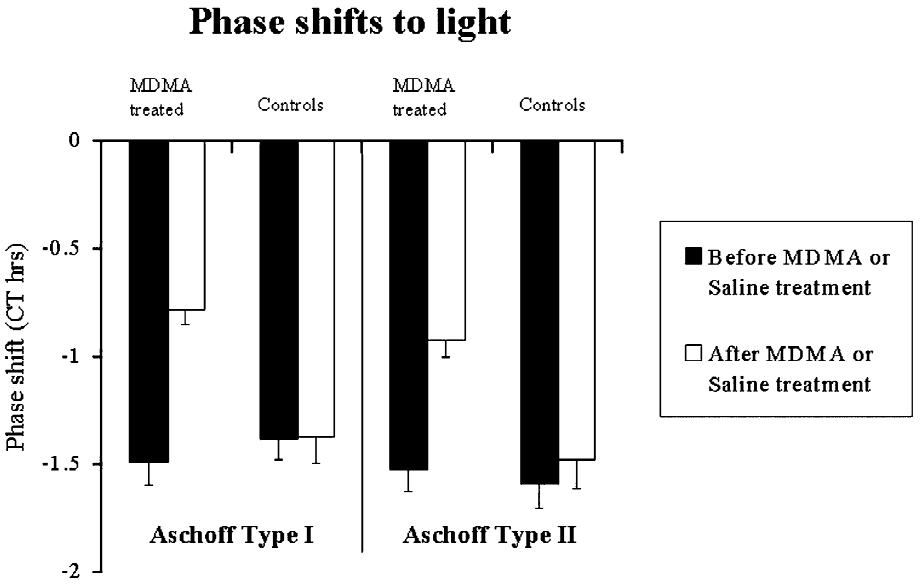

Fig. 3. Histograms depicting differences in mean phase shifts to a light pulse before and after treatment with MDMA under an Aschoff Type I and II paradigm. Standard error of the means are included.

interaction ($F_{(1,11)}=9.28$, $P<0.05$). Hamsters phase shifted significantly less to the 15 min of light after being treated with MDMA (Tukey HSD, $P<0.001$).

4. Discussion

MDMA is a known selective serotonin neurotoxin in animals and possibly humans [40,28,3]. Published literature has shown that the serotonergic system is involved in photic and non-photic phase shifting of the circadian clock. The current study aimed to investigate whether repeated exposure to MDMA would alter the phase shifting response of the Syrian hamster to the serotonin 5-HT1A/7 receptor agonist 8-OH-DPAT. The study also investigated the ability of the circadian clock to phase shift to a light pulse after treatment with MDMA. Phase shifts to the 5HT1A/7 receptor agonist 8-OH-DPAT at CT8 or ZT8 were significantly attenuated by pretreatment with MDMA. In addition pretreatment with MDMA significantly attenuated phase shifts to a light pulse at CT14 or ZT14.

Previous research using an Aschoff Type II procedure has shown that the transition from the light–dark cycle into constant darkness produces a phase shift of its own. It has been shown that in saline controls, the phase shift from LD to DD was approximately 30 CT min [8]. It is likely that a portion of the phase shifts to 8-OH-DPAT in the current study may also be attributed to the change in lighting conditions. However the transition from LD to DD in the Aschoff Type II paradigm had no effect on the magnitude of phase shifts to light in the current study.

There is a dense serotonergic input to the SCN from the midbrain raphe [2,25]. The median raphe (MR) innervates the SCN, whereas the dorsal raphe (DR) innervates the IGL [19]. Photic information is conveyed to the SCN via two pathways, a direct pathway from the retina via the retinohypothalamic tract [17] and an indirect pathway from the geniculohypothalamic tract, via a projection from the IGL [29]. MDMA could attenuate phase shifts to a serotonin agonist and light by acting in a variety of locations, including the SCN, the MR and/or the DR.

MDMA may alter phase shifts to non-photic and photic stimuli by actions within the SCN. It has been shown that local administration of 8-OH-DPAT into the SCN induced phase advances of the pacemaker during the subjective day [10]. In addition, timed microdialysis perfusions of the SCN with 8-OH-DPAT, advances the clock [12]. Therefore the phase shifting effect of 8-OH-DPAT may be mediated by either the 5-HT1A or 7 receptors in the SCN area [11]. The SCN contain moderate concentrations of 5-HT1A receptors [35] and 8-OH-DPAT may exert its effect through a direct action at this site ([10] but see Ref. [21]). The 5HT7 receptor subtype is also concentrated in the region of the SCN, as 8-OH-DPAT induced phase advances in vivo can be suppressed by administration of the specific 5-HT7 receptor antagonist ritanserin ([12] but see Ref. [13]). Immunocytochemical techniques have localised this subtype at GABA terminals in the mouse SCN [4]. Furthermore in rats, 8-OH-DPAT can reset the circadian clock in vitro [30] and pretreatment with MDMA attenuates phase advances to this serotonin agonist [7]. It is therefore possible that MDMA alters the response of the circadian pacemaker to the non-photic stimulus 8-OH-DPAT by altering the number and/or the distribution of 5-HT1A and/or the 5-HT7 receptors at the level of the SCN.

Alternatively, the attenuation of phase shifts to 8-OH-DPAT by MDMA may be due to damage of serotonergic

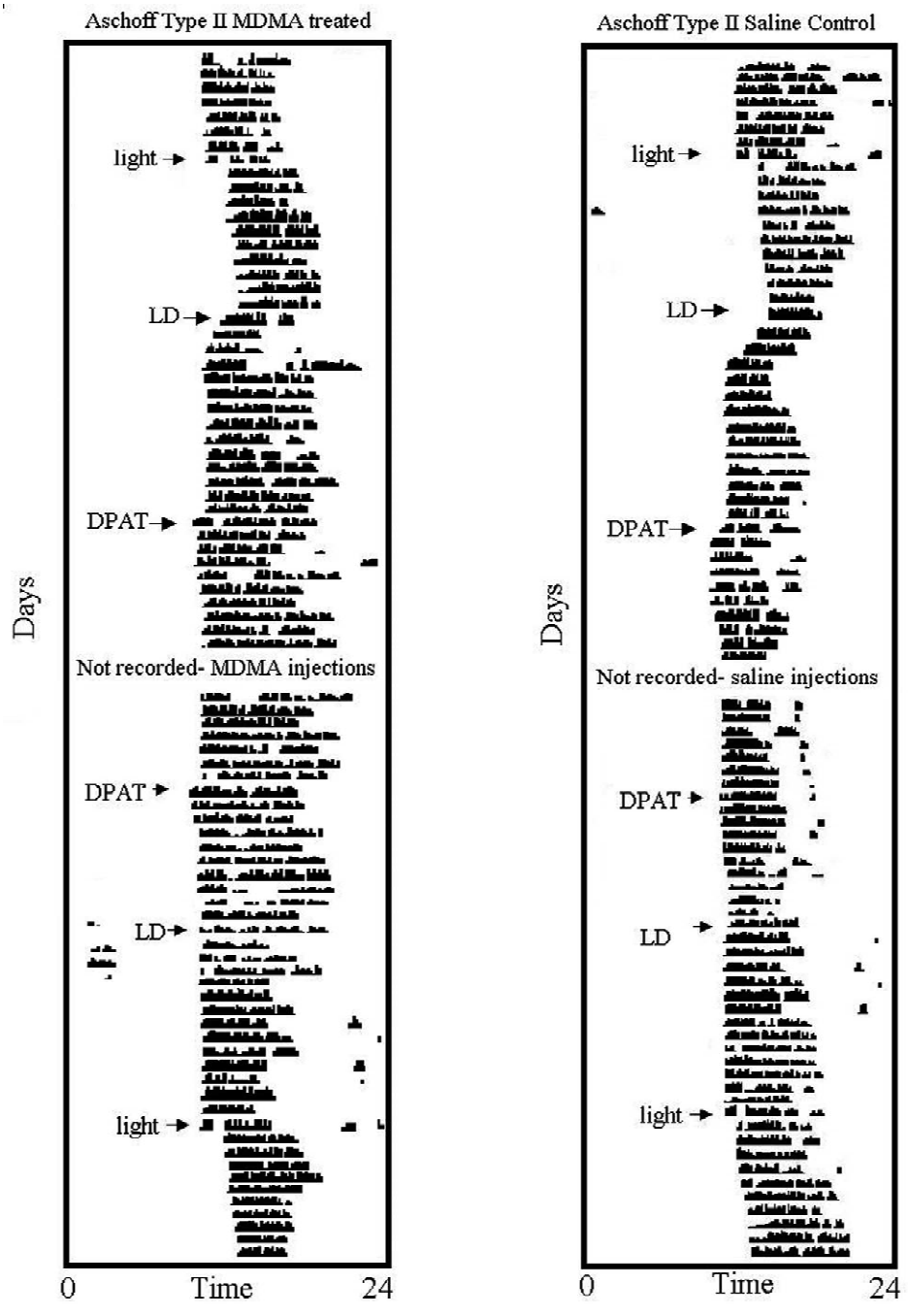

Fig. 4. Representative actograms illustrating phase shifts to 8-OH-DPAT at ZT8 and light at ZT14 before and after treatment with MDMA under an Aschoff Type II paradigm. The vertical of the actogram shows days as the experiment progressed and the horizontal represents the 24-h time period. The arrow denotes pulse day.

input from the median raphe. Data suggests that 8-OH-DPAT may act to phase shift the circadian clock when microinjected directly into the raphe [21]. Furthermore by destroying 5-HT fibres connecting the MR to the SCN it was shown that phase shifts to peripherally administered 8-OH-DPAT were abolished [36]. Therefore it is possible that damage to this pathway could explain why phase shifts to a serotonin agonist were attenuated in our study.

Experimental evidence has suggested that the serotonergic system is involved in the synchronisation of the pacemaker to light [32,41,10,33] and therefore it is possible that MDMA is acting at the level of the SCN to attenuate phase shifts to light. Local administration of the serotonin 5HT1A/7 receptor agonist 8-OH-DPAT into the SCN, inhibits phase advances to light [41]. In addition systemic administration of 8-OH-DPAT inhibits both phase delays and advances of the circadian pacemaker to light [32]. While serotonin agonists have been shown to inhibit

phase shifts to light, the serotonin neurotoxin 5,7 DHT potentiates phase shifts to light in mice and hamsters [9,24]. Based on this previous work, we may have predicted an increase in phase shifts to light after administration of the neurotoxin MDMA; however we saw a significant decrease in phase shifts to light. Neurotoxic agents target and deplete neurons in various brain regions. MDMA is known to selectively deplete 5-HT axons and axon terminals [40] whereas 5,7 DHT is thought to destroy cell bodies [24]. This differing pattern of serotonergic neurotoxicity may provide clues as to the reason for the differences seen between the MDMA-induced attenuation of phase delays and previous reports that a 5-HT neurotoxin caused increases in phase delays to light.

Finally, damage may occur to the connections between the dorsal raphe fibres and the intergeniculate leaflet and this may indirectly alter the response of another neurotransmitter necessary for phase shifts to non-photic and photic stimuli. The dorsal raphe provides an indirect pathway via the IGL to the SCN [19]. Bilateral injection of 8-OH-DPAT into the IGL induced phase advances of the circadian rhythm [10]. In addition lesions of the IGL block 8-OH-DPAT-induced phase shifts [37]. This suggests an indirect role of the IGL in phase shifts to 8-OH-DPAT. Intergeniculate leaflet neurons that project to the SCN contain neuropeptide Y (NPY) and γ-aminobutyric acid (GABA) [15,23]. It may be that MDMA alters 5-HT innervation from the DR to the IGL. Alteration in the amount of 5-HT released in this pathway could result in the disinhibition of the IGL, causing a subsequent release of neurotransmitters such as GABA and/or NPY into the SCN [21,1].

GABAergic neurons have a prominent role in the modulation of the circadian clock. The majority of the SCN neurons are GABAergic [23]. Alteration of GABA transmission has been shown to modulate non-photic and photic shifts of the clock. For example, 8-OH-DPAT-induced phase advances can be blocked by administration of bicuculline [21]. In addition, phase delays to light were attenuated by GABAa and GABAb agonists [14]. Disinhibition of GABA release into the SCN may be a possible, if not complex explanation for the decrease phase shifts to light in the present study.

Neuropeptide Y is also thought to be involved in non-photic and photic phase shifting of the clock. The phase shifting effect of 8-OH-DPAT can be blocked by NPY in rats in vitro [31]. Thus increased NPY into the SCN may explain the observed decreased phase shifts to 8-OH-DPAT in the present study. Furthermore NPY attenuates phase shifts to glutamate in vitro and also blocked light-induced phase delays of the circadian rhythm [6,42]. Therefore it is possible that increased release of NPY into the SCN may explain the attenuation of phase shifts to 8-OH-DPAT and light seen in our study.

In conclusion, these experiments have shown that MDMA alters the behavioural response of the Syrian hamster to phase shift to a serotonin agonist and to a photic stimulus. The most reasonable explanation based on the evidence may be that MDMA damages serotonergic innervation from the dorsal raphe pathway, which indirectly alters the response of other neurotransmitters necessary for resetting of the circadian clock. Further studies to identify anatomically where MDMA damage occurs are necessary before any firm conclusions can be made. We have established that MDMA alters clock function. Our findings support recent work, which demonstrate that MDMA alters the ability of the circadian clock to phase shift to a serotonin agonist [7]. Disruption of the circadian system has been linked with a variety of disorders such as sleep, mood and concentration difficulties and depression consequently outlining the potential dangers of long-term ecstasy use.

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