



Published in final edited form as:

Psychopharmacology (Berl). 2017 August ; 234(15): 2277–2287. doi:10.1007/s00213-017-4654-1.

Assessment of tolerance to the effects of methamphetamine on daytime and nighttime activity evaluated with actigraphy in rhesus monkeys

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Abstract

Rationale—Methamphetamine is one of the most largely consumed illicit drugs, and its use is associated with abuse liability and several adverse health effects, such as sleep impairment. Importantly, sleep quality can influence addiction treatment outcomes. Evidence suggests that tolerance can develop to the sleep-disrupting effects of stimulant drugs.

Objective—The aim of the present study was to investigate the development of tolerance to the actigraphy-based sleep-disrupting and stimulant effects of methamphetamine self-administration in rhesus monkeys.

Methods—Methamphetamine (0.03 mg/kg/inf, i.v.) self-administration was carried out following 3 different protocols: 14 consecutive days of self-administration; 5 days per week for 3 weeks, with a 2-day interval between 5-day blocks of self-administration; and 3 days per week for 3 weeks, with a 4-day interval between 3-day blocks of self-administration. Daytime activity and activity-based sleep measures were evaluated with Actiwatch monitors a week before (baseline parameters) and throughout each protocol.

Results—Methamphetamine self-administration markedly disrupted sleep-like measures and increased daytime activity. Tolerance developed to those effects with repeated methamphetamine intake exceeding 5 consecutive days. Inclusion of washout periods (2 or 4 days) between blocks of methamphetamine self-administration attenuated the development of tolerance, with longer breaks from methamphetamine intake being more effective in maintaining the sleep-disrupting and stimulant effects of methamphetamine.

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Conflict of Interest

The authors declare no conflict of interest.

Conclusions—Tolerance can develop to the stimulant and sleep-disrupting effects of methamphetamine self-administration. Interruption of drug intake extends the effects of methamphetamine on sleep-like measures and daytime activity.

Keywords

methamphetamine; sleep; self-administration; activity; actigraphy; rhesus monkeys

Introduction

According to the United Nations Office on Drugs and Crime (UNODC), the use of amphetamine-type stimulants has become widespread in the past decades, with the global number of users having reached nearly 35.7 million people in 2014 (UNODC 2016). Among these drugs, methamphetamine has accounted for the largest increase in the use and availability of amphetamine-type stimulants in the past 5 years (UNODC 2016).

Amphetamine-type stimulants are largely consumed for recreational purposes, mainly due to the ease of access to these drugs. As alertness-enhancing and stimulant drugs, amphetamines are the active ingredient in several products currently approved for medical use (Mitler et al. 1993; Morgenthaler et al. 2007; Barateau et al. 2016; Briars and Todd 2016). Amphetamines are also illicitly consumed in order to promote wakefulness due to professional demands, such as in shift workers (Bonfond et al. 2004) and truck drivers (Giroto et al. 2014).

The broad pharmacological actions of amphetamines translate into the generation of adverse effects and abuse liability. Currently, the abuse of amphetamine-type stimulants is a global public health problem (UNODC 2016), and their use is associated with numerous adverse physical, behavioral, and mental health outcomes (Herbeck et al. 2015; Rommel et al. 2015). Disturbed sleep is one of the main adverse effects of the use of amphetamine-type stimulants (Cruickshank and Dyer 2009). Sleep impairment has been associated with the use of amphetamines in the clinics (Huang et al. 2011; Santisteban et al. 2014; Mitler et al. 1993; Barateau et al. 2016), as well as in the context of amphetamine and methamphetamine ongoing abuse (Kirkpatrick et al. 2012a; Mahoney et al. 2014).

Evidence suggests that tolerance can develop to the sleep-disrupting effects of stimulant drugs. Studies conducted in children with attention deficit hyperactivity disorder (ADHD) indicate that while treatment with stimulants continued to exert therapeutic effects for up to 5 years, tolerance developed to some adverse effects, including subjective daytime sleepiness and fatigue (Huang and Tsai 2011). In addition, tolerance has been reported to the sleep-disrupting effects of methamphetamine following repeated (up to 3 consecutive days) administration of low oral doses in healthy humans, a phenomenon that was accompanied by the development of tolerance to methamphetamine's positive subjective effects (Comer et al. 2001; Kirkpatrick et al. 2012a). However, it remains unclear whether tolerance can develop to the sleep-disrupting effects of psychostimulants in the context of drug abuse.

Sleep quality directly influences addiction treatment outcomes, with individuals with history of sleep problems showing a higher risk of relapse and for the development of drug abuse (Ford and Kamerow 1989; Brower and Perron 2010; Wong et al. 2010; Hasler et al. 2012). Sleep patterns should always be considered in treatment strategies, emphasizing the

importance of investigating the factors influencing the time course of stimulant-induced sleep impairment. Thus, the aim of the present study was to investigate the development of tolerance to the stimulant and sleep-disrupting effects of methamphetamine self-administration (SA) in rhesus monkeys and the influence of the drug regimen on this phenomenon.

Material and Methods

Subjects

Three adult male (ROf8, RLk4 and RJ18) and 2 adult female (RVm8 and RZs9) rhesus monkeys (*Macaca mulatta*) weighing 9–15 kg, served as subjects for the studies. Animals were fitted with collars (Primate Products) prior to the initiation of the studies. Each subject was individually housed in stainless steel home cages and fed Purina monkey chow (Ralston Purina, St. Louis, MO), supplemented with fruit and vegetables daily. Water was continuously available in the colony. Environmental enrichment was provided on a regular basis. The colony was maintained at an ambient temperature of $22\pm 2^{\circ}\text{C}$ at 45–50% humidity, and the lights were set to a 12-h light/dark cycle (lights on at 7h; lights off at 19h). All subjects had a long history of exposure to methamphetamine, having consistently self-administered methamphetamine 5–7 days a week for the past 4 years, except for weeks when SA was discontinued between the end of a protocol and the beginning of a new experiment (Andersen et al. 2013; Berro et al. 2016). All protocols and animal care and handling strictly followed the National Institutes of Health Guide for the Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985) and the recommendations of the American Association for Accreditation of Laboratory Animal Care, and were approved by the Institutional Animal Care and Use Committee of Emory University.

Drugs

(+/-) Methamphetamine hydrochloride was provided by the National Institute on Drug Abuse (Bethesda, MD, USA), and was dissolved in 0.9% sterile physiological saline and administered intravenously. The drug dose was calculated and is expressed as the salt form.

Self-administration

All animals were surgically prepared under sterile conditions with a chronic indwelling venous catheter implanted in a major vein (femoral or jugular) and attached to a subcutaneous vascular access port, as previously described (Howell and Wilcox 2001). The apparatus and SA procedure were previously described by Howell and Wilcox (2001). Animals were trained to respond under a fixed ratio (FR) 20 schedule of drug delivery. Subjects had the opportunity to self-administer methamphetamine during 60-min sessions once a day, 3–7 days/week in the morning (starting between 8–10am). The animals were positioned in a primate chair (Primate Products) and placed in a sound-attenuating experimental chamber for the duration of the session and maintained in their home-cages for the remainder of the day. During the test session, the operant panel was illuminated with a white light which served as a discriminative stimulus. Completion of the FR 20 resulted in a change in the stimulus light from white to red for 15s and a methamphetamine infusion (0.03 mg/kg in 0.5 ml infused over 3s). This infusion was followed by a 60-s timeout. At the

end of the timeout, the white light was presented again to signal the opportunity to complete another FR. Methamphetamine intake was determined as the number of infusions received on a given session times the unit dose (0.03 mg/kg/inf).

Daytime and nighttime activity

Actiwatch sensors (Mini Mitter, Bend, OR, USA) were used to assess daytime and nighttime activity, as previously described (Andersen et al. 2010, 2013). Subjects had been adapted to wearing the activity monitors and trained to cooperate with the attachment of the sensor in their collars. Daytime activity data generated activity counts/hour. Nighttime activity data generated the following sleep-like behavior parameters: sleep efficiency (i.e., the percentage of the dark phase spent sleeping); sleep latency (i.e., the time between the lights-off time and the first sleep bout); fragmentation index (i.e., the number of immobile bouts during the dark phase that lasted less than 1 min during the sleep recording period). Sleep-like measures were solely derived from behavioral measures. All parameters were calculated using the Actiware Sleep 3.4 software program (Mini-Mitter, Bend, OR, USA).

Protocol design

Before the beginning of drug SA, Actiwatches were attached to the monkeys' collars and baseline sleep-like behavior was measured for 1 week. Activity recording continued for the duration of the experiments. Methamphetamine SA was carried out following 3 different protocols: 14 consecutive days of SA (14 protocol); 5 days per week during 3 weeks, with a 2-day interval between 5-day blocks of SA, in a total of 15 days of methamphetamine SA across 21 days (5–2 protocol); 3 days per week during 3 weeks, with a 4-day interval between 3-day blocks of SA, in a total of 9 days of methamphetamine SA across 21 days (3–4 protocol). SA was discontinued after the end of each protocol and sleep-like measures continued for an additional baseline week between experimental protocols.

Data analysis

Within an experimental protocol (14 Protocol, 5–2 Protocol or 3–4 Protocol), the data were combined for the beginning (5 or 3 first days) and the end (5 or 3 last days) of the SA protocol. All data were analyzed using one-way repeated-measures (RM) analysis of variance (ANOVA) corrected for multiple comparisons using Dunnett's test to indicate significance. Correlational analyses were conducted using Pearson's Correlation. All graphical data presentations were created using Prism 5 (GraphPad Software), and all statistical tests were performed using PASW Statistics 18 (SPSS Statistics Software). Significance was accepted at an alpha of 0.05.

Results

Methamphetamine self-administration

Methamphetamine (0.03 mg/kg/infusion) reliably maintained responding in all 5 subjects, with individual average drug intake ranging from 0.36 to 1.38 mg/kg/session and a group mean of 0.81 ± 0.05 mg/kg/session. Drug intake remained stable across days within an experimental protocol, as well as between protocols. One-way RM ANOVA across the different days of methamphetamine SA showed no significant differences on

methamphetamine intake (14 Protocol [F(4,69)=1.32, $p>0.05$], Fig. 1A; 5–2 Protocol [F(4,69)=2.57, $p>0.05$], Fig. 1B; 3–4 Protocol [F(4,69)=0.7, $p>0.05$], Fig. 1C). Pearson's Correlation analysis showed no correlation between methamphetamine intake and sleep disruption or daytime activity levels under any of the protocols.

Sleep-wake pattern

Sleep-like measures—Sleep-like measures are presented as normalized data (percentage of baseline). Individual-subject baseline sleep-like parameters are shown in Table 1.

Sleep efficiency: For the 14 Protocol, 1-way RM ANOVA corrected for multiple comparisons using Dunnett's test showed a significant decrease in sleep efficiency on the first 5 days, but not the last 5 days, of methamphetamine SA compared to baseline [F(4,14)=7.93, $p<0.05$] (Fig. 2A). Analysis of the different days of methamphetamine SA indicated a significant decrease in sleep efficiency on days 2–4 of SA compared to baseline [F(4,74)=2.33, $p<0.05$] (Fig. 2B). For the 5–2 Protocol, 1-way RM ANOVA corrected for multiple comparisons using Dunnett's test showed a significant decrease in sleep efficiency on the first 5 days, but not the last 5 days, of methamphetamine SA compared to baseline [F(4,14)=8.95, $p<0.01$] (Fig. 2C). Analysis of the different days of methamphetamine SA indicated a significant decrease in sleep efficiency on days 2–4 and 9–11 of SA compared to baseline [F(4,74)=2.33, $p<0.05$] (Fig. 2D). For the 3–4 Protocol, 1-way RM ANOVA corrected for multiple comparisons using Dunnett's test showed a significant decrease in sleep efficiency for all methamphetamine SA blocks compared to baseline [F(4,14)=10.7, $p<0.001$] (Fig. 2E). Analysis of the different days of methamphetamine SA indicated a significant decrease in sleep efficiency on days 2–3, 8–10 and 15–16 of SA compared to baseline [F(4,74)=4.91, $p<0.0001$] (Fig. 2F).

Sleep Latency: For the 14 Protocol, 1-way RM ANOVA corrected for multiple comparisons using Dunnett's test showed a significant increase in sleep latency on the first 5 days, but not the last 5 days, of methamphetamine SA compared to baseline [F(4,14)=7.65, $p<0.01$] (Fig. 3A). Analysis of the different days of methamphetamine SA indicated a significant increase in sleep latency on days 1–4 of SA compared to baseline [F(4,74)=4.9, $p<0.0001$] (Fig. 3B). For the 5–2 Protocol, 1-way RM ANOVA corrected for multiple comparisons using Dunnett's test showed a significant increase in sleep latency on the first 5 days, but not the last 5 days, of methamphetamine SA compared to baseline [F(4,14)=4.03, $p<0.05$] (Fig. 3C). Analysis of the different days of methamphetamine SA indicated a significant increase in sleep latency on days 1–4 and 8–10 of SA compared to baseline [F(4,74)=4.16, $p<0.0001$] (Fig. 3D). For the 3–4 Protocol, 1-way RM ANOVA corrected for multiple comparisons using Dunnett's test showed a significant increase in sleep latency for all methamphetamine SA blocks compared to baseline [F(4,14)=3.79, $p<0.05$] (Fig. 3E). Analysis of the different days of methamphetamine SA indicated a significant increase in sleep latency on days 1–3, 8–10 and 15–17 of SA compared to baseline [F(4,74)=2.67, $p<0.001$] (Fig. 3F).

Sleep Fragmentation: For the 14 Protocol, 1-way RM ANOVA corrected for multiple comparisons using Dunnett's test showed a significant increase in sleep fragmentation on the first 5 days, but not the last 5 days, of methamphetamine SA compared to baseline

[F(4,14)=3.75, $p<0.05$] (Fig. 4A). Analysis of the different days of methamphetamine SA indicated a significant increase in sleep fragmentation on days 1–5 of SA compared to baseline [F(4,74)=4.48, $p<0.0001$] (Fig. 4B). For the 5–2 Protocol, 1-way RM ANOVA corrected for multiple comparisons using Dunnett's test showed a significant increase in sleep fragmentation for all methamphetamine SA blocks compared to baseline [F(4,14)=23.56, $p<0.0001$] (Fig. 4C). Analysis of the different days of methamphetamine SA indicated a significant increase in sleep fragmentation on days 1–5, 8–10 and 16 of SA compared to baseline [F(4,74)=6.03, $p<0.0001$] (Fig. 4D). For the 3–4 Protocol, 1-way RM ANOVA corrected for multiple comparisons using Dunnett's test showed a significant increase in sleep fragmentation for all methamphetamine SA blocks compared to baseline [F(4,14)=6.76, $p<0.05$] (Fig. 4E). Analysis of the different days of methamphetamine SA indicated a significant increase in sleep fragmentation on days 1–3, 8–10 and 16–17 of SA compared to baseline [F(4,74)=2.59, $p<0.01$] (Fig. 4F).

Daytime activity measures—Averaged daytime activity data (activity counts/hour) were combined across the 12h daytime period (7h–19h) and are presented as normalized data (percentage of baseline). Individual-subject baseline daytime activity are expressed as mean \pm SEM; individual subject codes followed by corresponding values were: ROf8: 6399 \pm 190; RVm8: 8595 \pm 478; RLk4: 12107 \pm 383; RZs9: 14545 \pm 508; RJl8: 11964 \pm 100. Daytime activity data are also presented as activity counts across the hours of the day after the SA sessions and before lights off (12h–18h).

For the 14 Protocol, analysis of the different days of methamphetamine SA indicated a significant increase in activity counts/hour on days 2–5 of SA compared to baseline [F(4,74)=3.92, $p<0.001$] (Fig. 5A). One-way RM ANOVA corrected for multiple comparisons using Dunnett's test of the averaged daytime activity data showed a significant increase in daytime activity on the first 5 days, but not the last 5 days, of methamphetamine SA compared to baseline [F(4,14)=4.35, $p<0.05$] (Fig. 5B). Two-way RM ANOVA of the activity counts at each hour during daytime indicated a significant effect of time [F(6,96)=11.67, $p<0.0001$] and treatment [F(4,16)=3.89, $p<0.05$], but no interaction. From hours 12–13, activity counts were higher for all methamphetamine SA blocks compared to baseline, while from hours 15–18 only activity counts for the first 5 days of methamphetamine SA were higher compared to baseline (Fig. 5B).

For the 5–2 Protocol, analysis of the different days of methamphetamine SA indicated a significant increase in activity counts/hour on days 2–5, 9–12, 16 and 19 of SA compared to baseline [F(4,74)=3.4, $p<0.0001$] (Fig. 5C). One-way RM ANOVA corrected for multiple comparisons using Dunnett's test of the averaged daytime activity data showed a significant increase in daytime activity on the first 5 days, but not the last 5 days, of methamphetamine SA compared to baseline [F(4,14)=4.46, $p<0.05$] (Fig. 5D). Two-way RM ANOVA of the activity counts at each hour during daytime indicated a significant effect of time [F(6,96)=25.19, $p<0.0001$] and treatment [F(4,16)=3.9, $p<0.05$], but no interaction. From hours 12–17, activity counts were higher for all methamphetamine SA blocks compared to baseline, while for hour 18 only activity counts for the first 5 days of methamphetamine SA were higher compared to baseline (Fig. 5D).

For the 3–4 Protocol, analysis of the different days of methamphetamine SA indicated a significant increase in activity counts/hour on days 2–3, 9–10 and 16–17 of SA compared to baseline [$F(4,74)=5.12$, $p<0.0001$] (Fig. 5E). One-way RM ANOVA corrected for multiple comparisons using Dunnett's test of the averaged daytime activity data showed a significant increase in daytime activity for all methamphetamine SA blocks compared to baseline [$F(4,14)=6.0$, $p<0.05$] (Fig. 5F). Two-way RM ANOVA of the activity counts at each hour during daytime indicated a significant effect of time [$F(6,96)=9.65$, $p<0.0001$] and treatment [$F(4,16)=6.88$, $p<0.05$], but no interaction. From hours 12–17 activity counts were higher for all methamphetamine SA blocks compared to baseline, while for hour 18 only activity counts for the 9 days and first 3 days of methamphetamine SA were higher compared to baseline (Fig. 5F).

Discussion

Results from the present study demonstrate that intravenous methamphetamine SA markedly disrupted sleep-like measures and increased daytime activity in rhesus monkeys. Tolerance developed to these effects with repeated methamphetamine intake exceeding 5 consecutive days. Inclusion of washout periods (2 or 4 days) between blocks of methamphetamine SA attenuated the development of tolerance over the days of methamphetamine SA, with longer breaks from methamphetamine intake being more effective in maintaining the sleep-disrupting and stimulant effects of methamphetamine.

During the first 3–5 days of methamphetamine SA, sleep-like behavior was disrupted in all 3 protocols, an effect that immediately dissipated after methamphetamine discontinuation (Protocols 5–2 and 3–4). These data are consistent with previous studies on the effects of stimulants on sleep. Studies from our group have shown that acute noncontingent amphetamine treatment disrupted sleep in rhesus monkeys (Murnane et al. 2013). We have also demonstrated that 5-day blocks of methamphetamine SA induced sleep disruption in rhesus monkeys, with sleep normalizing immediately after drug discontinuation (Andersen et al. 2013). Studies in healthy humans have also shown decreases in subjective and objective sleep measures after acute methamphetamine administration (Comer et al. 2001; Kirkpatrick et al. 2012a), with sleep returning to normal baseline levels (no evidence of residual effects) following active methamphetamine (Comer et al. 2001). Importantly, studies conducted in experienced methamphetamine users also found marked decreases in sleep measures after acute methamphetamine administration (Perez et al. 2008; Kirkpatrick et al. 2012b). These results indicate that frequent use does not blunt the acute drug effects on sleep, corroborating the present findings in monkeys with a long history of exposure to methamphetamine.

Methamphetamine SA also had marked stimulant effects on daytime activity. Subjects showed an increase in general activity from days 2 through 3–5 of drug intake. Although subjects did not express significantly higher daytime activity compared to baseline on the first day of methamphetamine SA, this effect was sensitized, with an increase in general daytime activity from days 2 through 3–5 of drug intake. The development of sensitization to the behavioral effects of psychostimulants has been extensively described in rodents, and is considered to be a hallmark of plasticity associated with drug abuse (Bradberry 2007).

Our findings corroborate extensive literature on repeated and single dose-induced locomotor sensitization to amphetamines in rodents (Saito et al. 2014; Fukushiro et al. 2012; Chinen et al. 2006). The literature on behavioral sensitization to psychostimulants in nonhuman primates, on the other hand, is sparse and has relied mainly on the evaluation of behavioral measures progressing from lower to higher doses (Bradberry 2007). Our results add to the literature by showing the development of a rapid locomotor sensitization to the stimulant effects of methamphetamine in rhesus monkeys.

According to our results, tolerance developed to both the sleep-disrupting and daytime stimulant effects of methamphetamine with repeated drug intake exceeding 5 consecutive days (14 Protocol). A decrease in sleep disruption occurred despite stable intake, indicating that attenuated effects on sleep-like behavior and daytime activity were not a result of lower methamphetamine consumption. In addition, although Protocol 3–4 resulted in less methamphetamine exposures (9 exposures compared to 14 and 15 for Protocols 14 and 5–2, respectively), that is not sufficient to explain the lack of tolerance under Protocol 3–4. On the 9th day of methamphetamine SA (day 9 of the 14 Protocol, day 14 of the 5–2 Protocol and day 17 of the 3–4 Protocol), the effects of methamphetamine on sleep-like behavior were still present only when animals were submitted to the 3–4 Protocol. Our findings corroborate previous clinical studies showing tolerance to methamphetamine-induced sleep disruption (Comer et al. 2001; Kirkpatrick et al. 2012a) and daytime stimulant effects (Kelly et al. 1991) following repeated administration of low single oral doses in humans. Studies have also shown tolerance to other behavioral effects of amphetamine-type stimulants, such as decreased anorexic effects (Bittner et al. 1981; Kraeuchi et al. 1985; White et al. 2010), and decreased effectiveness in children chronically treated for ADHD (Ross et al. 2002).

The development of tolerance to the anorexic and attention-related effects of amphetamines can be prevented by increasing the drug dosage (Ross et al. 2002; White et al. 2010). The same seems to apply to the sleep-disrupting and stimulant effects of amphetamines. A previous study conducted in children with ADHD has shown that when subjects were given amphetamine daily with dose increasing weekly for 3 weeks, amphetamine treatment had marked long-lasting dose-dependent effects on sleep, with no signs of tolerance (Santisteban et al. 2014). Mitler and colleagues (1993) have shown that treatment with methamphetamine also caused a dose-dependent stimulant effect on daytime behavior and improvement in performance tasks in both narcoleptics and control individuals with no signs of tolerance. Because our experiments were conducted with contingent methamphetamine administration, we were not able to evaluate the effects of increasing drug dosage on the development of tolerance to the effects of methamphetamine. Nevertheless, our data provide primary evidence that inclusion of washout periods between methamphetamine SA also prevents the development of tolerance to both the sleep-disrupting and the daytime stimulant effects of methamphetamine over the days of drug SA.

A recent study that seems to be the first report of methamphetamine pharmacokinetic parameters in rhesus monkeys indicated that the half-life of methamphetamine is of approximately 3.2h in rhesus monkeys when given intramuscularly, while plasma levels of the methamphetamine metabolite amphetamine peak at 5h post-methamphetamine (Banks et al. 2016). On the other hand, methamphetamine is known to have a half-life of

approximately 12h in humans for smoked, intravenous and oral drug administration, with a peak in amphetamine levels 10–24 hours after methamphetamine and still detectable after 48 hours in humans (Cook et al. 1992, 1993). Although there are no reports of intramuscular methamphetamine pharmacokinetics in humans for comparison, human studies with intravenous methamphetamine administration suggest that the effects of methamphetamine and/or its metabolite amphetamine under our experimental conditions could be longer than those observed by Banks and colleagues (2016). It is important to note, however, that although the development of tolerance to the sleep-disrupting effects of methamphetamine was accompanied by tolerance to the daytime stimulant effects of the drug, these effects were not a function of drug intake in the present study. Further studies are necessary in order to investigate the mechanisms underlying the wake-promoting and sleep-disrupting effects of methamphetamine.

In summary, the present study provides evidence of the development of tolerance to the stimulant and sleep-disrupting effects of methamphetamine, and that inclusion of washout periods between blocks of drug intake can prevent this phenomenon. It has been previously reported that the average frequency of use of methamphetamine among chronic users is about 5 times per week, being lower in males (about 2 times per week) than in females (about 6 times per week) (Suwannachom et al. 2015). In another study conducted with methamphetamine users, 75.6% out of 189 participants reported using methamphetamine no more frequently than 9 times per month (Ding et al. 2014). Preclinical evidence from the present study indicate that the pattern and frequency of use of methamphetamine in humans would be associated with long-term effects on daytime activity and sleep. Because sleep impairment is considered a risk factor for drug relapse and for the development of drug abuse (Ford and Kamerow 1989; Brower and Perron 2010; Wong et al. 2010; Hasler et al. 2012), treatment strategies should focus on sleep as a contributing factor for methamphetamine abuse.

Acknowledgments

The authors thank Juliet Brown, Lisa Neidert and Melis Odabas-Geldiay for their excellent assistance with the experiments. This research was supported by USPHS Grants DA10344 (LLH), DA031246 (LLH) and ODP51OD11132 (Yerkes), AFIP and FAPESP Grant 2015/25482-3 (LFB).

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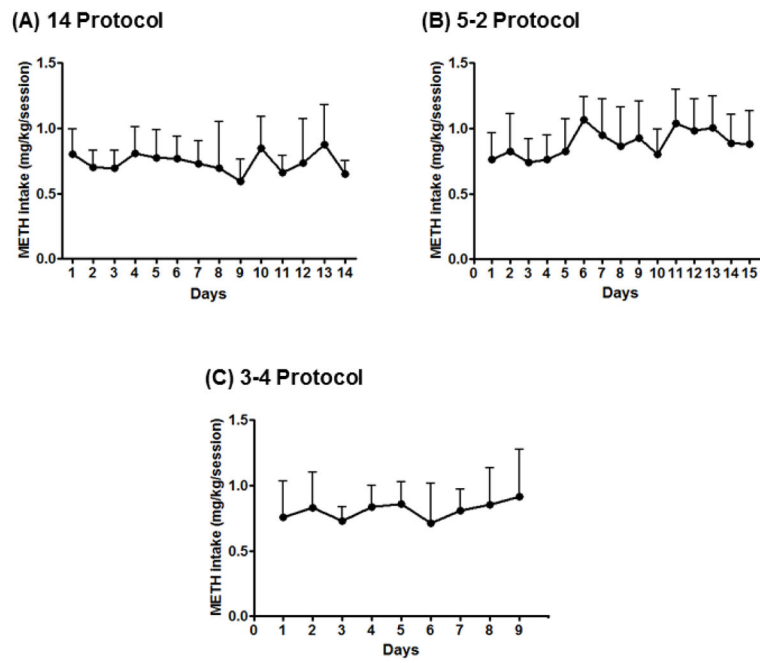


Figure 1. Methamphetamine intake (mg/kg/session) across days of methamphetamine self-administration (0.03 mg/kg/infusion, i.v.) for the 14 Protocol (A), the 5–2 Protocol (B) and the 3–4 Protocol (C). Data are expressed as Mean \pm SEM.

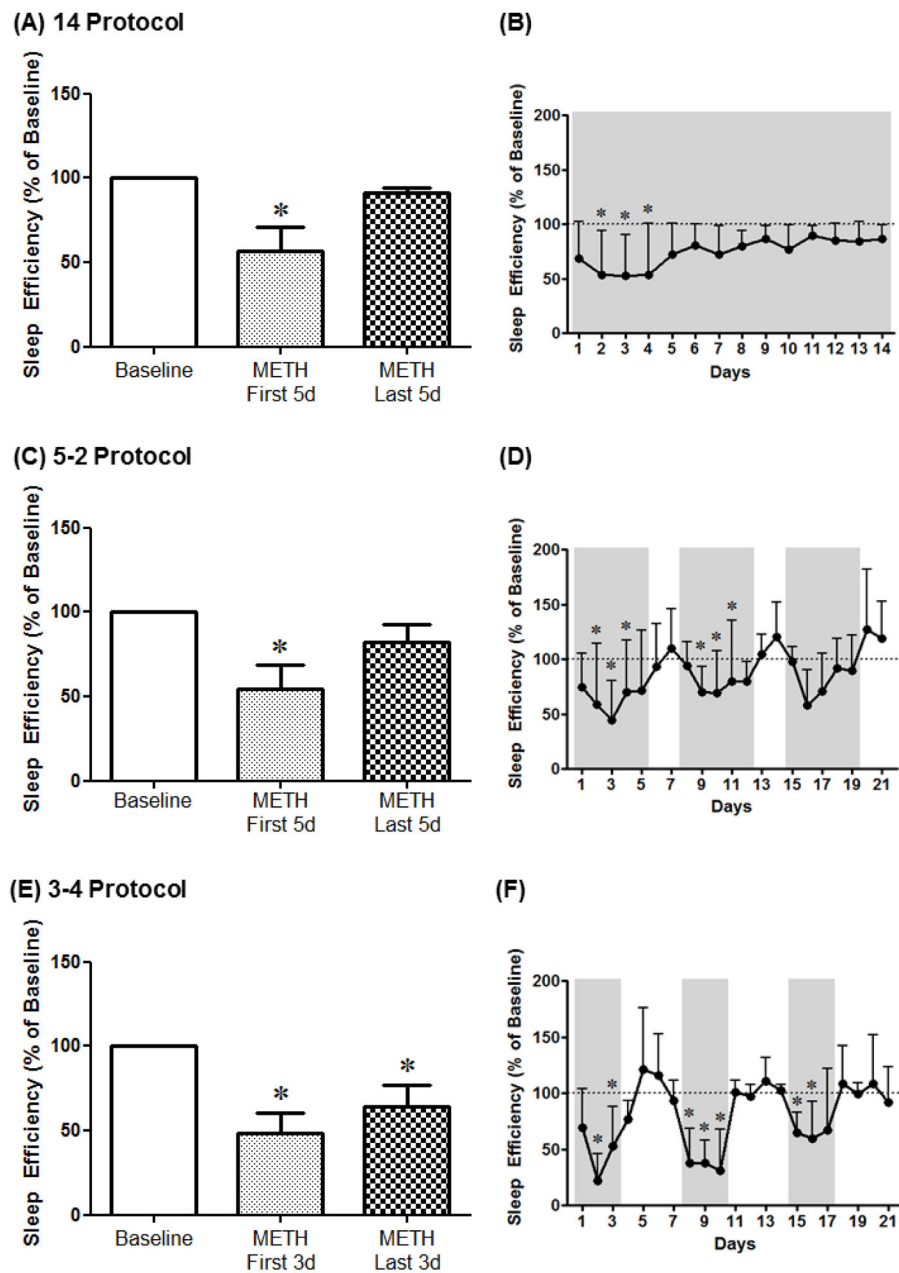


Figure 2. Sleep efficiency averaged across the first days (METH First 5d and METH First 3d) or the last days (METH Last 5d and METH Last 3d) of methamphetamine self-administration (0.03 mg/kg/infusion, i.v.) as well as across protocol days for the 14 Protocol (A, B), the 5–2 Protocol (C, D) and the 3–4 Protocol (E, F). Data are expressed as Mean \pm SEM. Dotted lines represent baseline sleep efficiency (100%). * $p < 0.05$ compared with baseline.

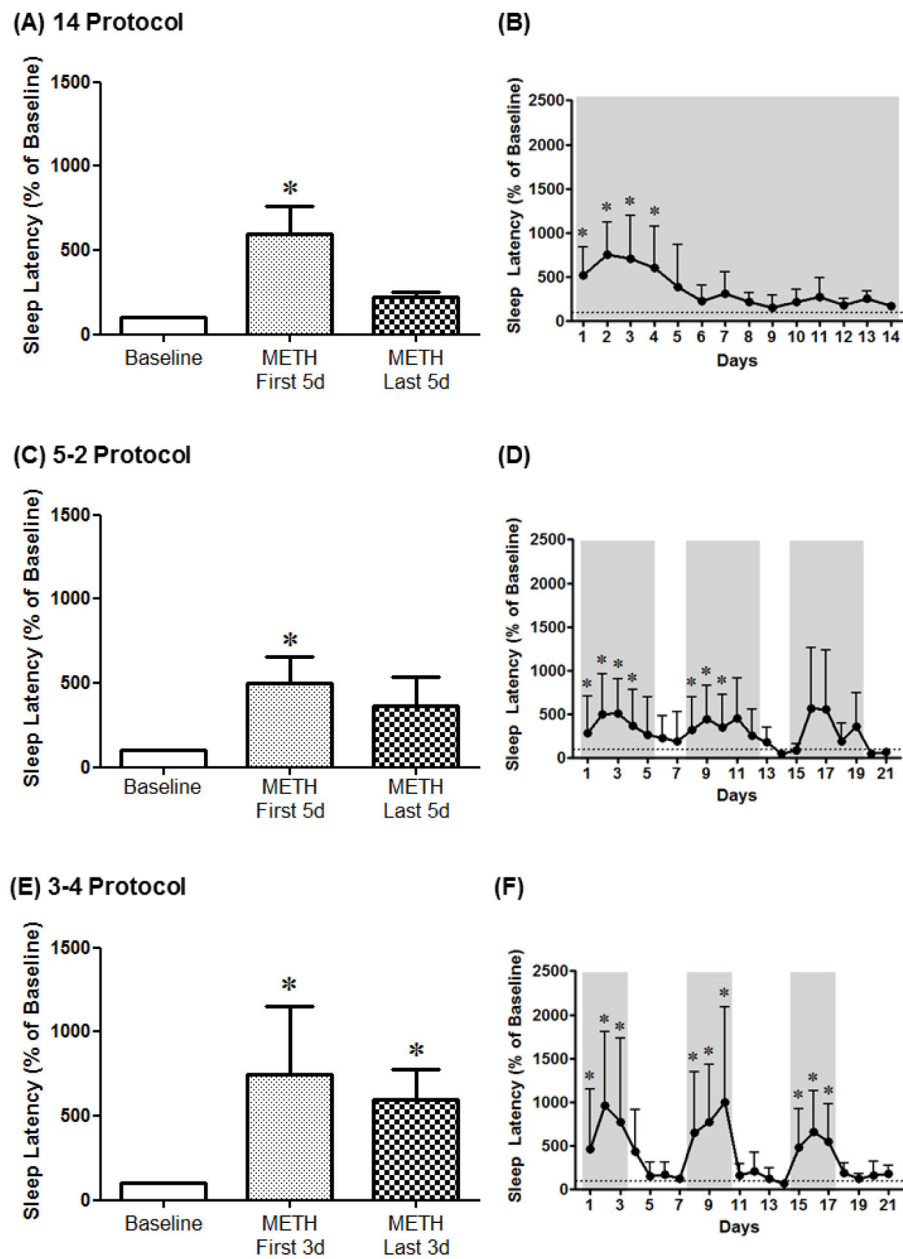


Figure 3. Sleep latency averaged across the first days (METH First 5d and METH First 3d) or the last days (METH Last 5d and METH Last 3d) of methamphetamine self-administration (0.03 mg/kg/infusion, i.v.) as well as across protocol days for the 14 Protocol (A, B), the 5–2 Protocol (C, D) and the 3–4 Protocol (E, F). Data are expressed as Mean \pm SEM. Dotted lines represent baseline sleep latency (100%). * $p < 0.05$ compared with baseline.

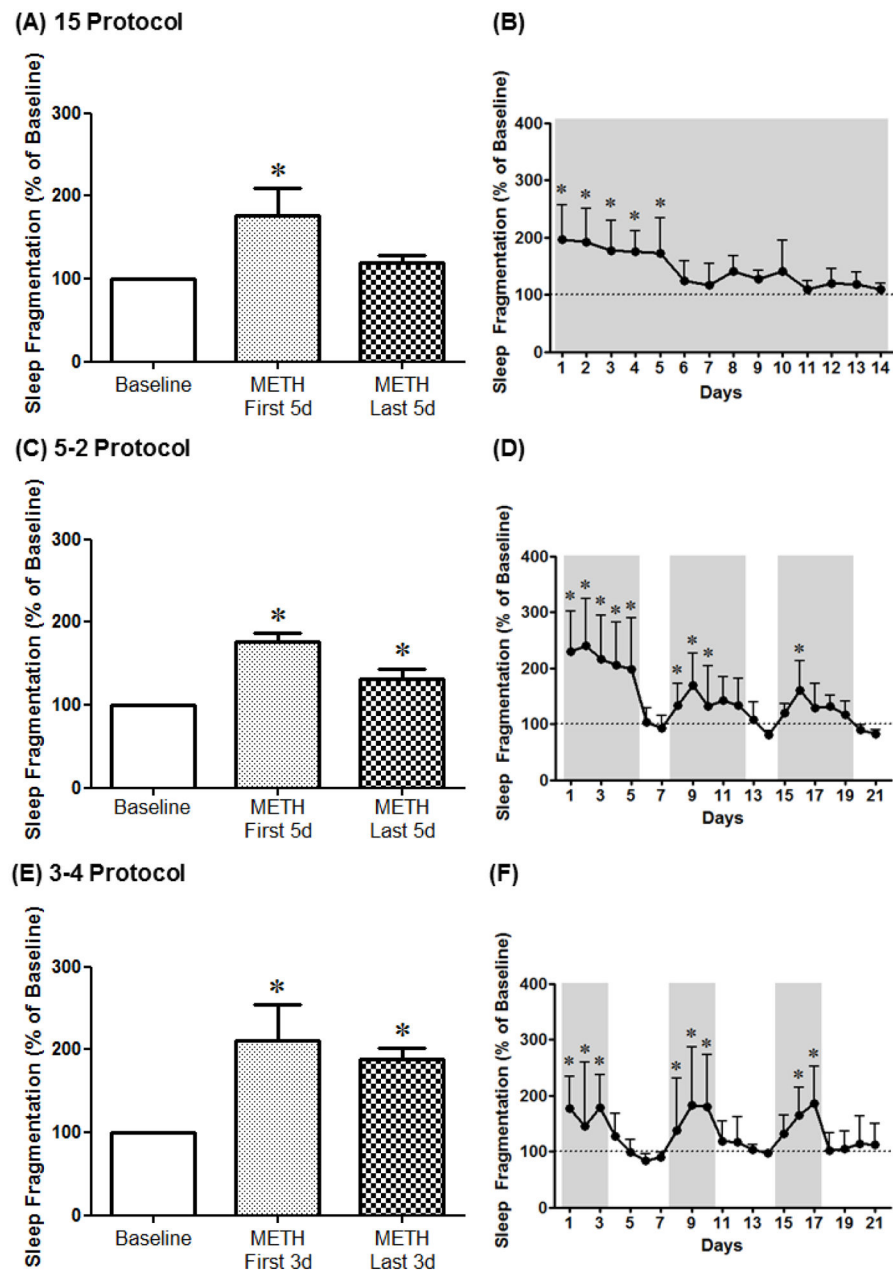


Figure 4. Sleep fragmentation averaged across the first days (METH First 5d and METH First 3d) or the last days (METH Last 5d and METH Last 3d) of methamphetamine self-administration (0.03 mg/kg/infusion, i.v.) as well as across protocol days for the 14 Protocol (A, B), the 5–2 Protocol (C, D) and the 3–4 Protocol (E, F). Data are expressed as Mean \pm SEM. Dotted lines represent baseline sleep fragmentation (100%). * $p < 0.05$ compared with baseline.

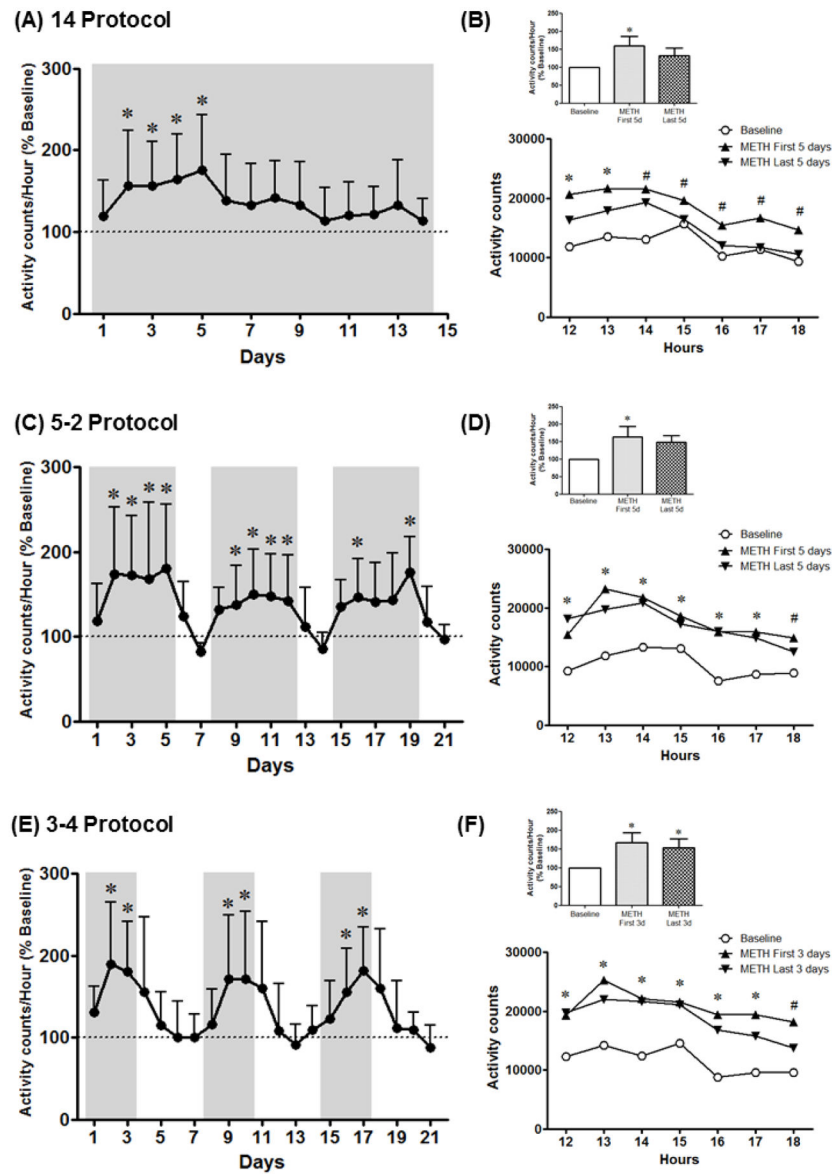


Figure 5. Daytime activity across protocol days for the 14 Protocol (A), the 5–2 Protocol (C) and the 3–4 Protocol (E). Daytime activity averaged across the first days (METH First 5d and METH First 3d) or the last days (METH Last 5d and METH Last 3d) of methamphetamine self-administration (0.03 mg/kg/infusion, i.v.) for the daytime period (7h–19h) as well as across daytime hours (12h–18h) for the 14 Protocol (B), the 5–2 Protocol (D) and the 3–4 Protocol (F). Data are expressed as Mean \pm SEM. Dotted lines represent baseline daytime activity (100%). * $p < 0.05$ compared with baseline for *all data points or # METH First 5 days.

Table 1

Individual-subject baseline sleep parameters

Subject	Sleep Efficiency (%)	Sleep Latency (min)	Fragmentation Index
ROf8 (M)	80.76±1.4	25.15±7.65	29.06±1.66
RVm8 (F)	70.20±0.42	66.47±1.27	59.37±0.45
RLk4 (M)	68.24±2.24	33.5±6.5	48.84±1.38
RZs9 (F)	46.93±3.51	126.75±65.98	83.95±2.78
RJ18 (M)	84.37±1.9	20.47±7.72	24.31±2.73

M = male rhesus monkey; F = female rhesus monkey. Data are expressed as mean ± SEM.

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