Effects of cocaine, methamphetamine and modafinil challenge on sleep rebound after paradoxical sleep deprivation in rats

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Sleep loss is both common and critically relevant to our society and might lead to the abuse of psychostimulants such as amphetamines, cocaine and modafinil. Since psychoactive substance abuse often occurs within a scenario of sleep deficit, the purpose of this investigation was to compare the sleep patterns of rats challenged with cocaine (7 mg/kg, *ip*), methamphetamine (7 mg/kg, *ip*), or modafinil (100 mg/kg, *ip*) subsequent to paradoxical sleep deprivation (PSD) for 96 h. Our results show that, immediately after 96 h of PSD, rats (10 per group) that were injected with a psychostimulant presented lower percentages of paradoxical sleep compared to those injected with saline (P < 0.01). Regarding slow wave sleep (SWS), rats injected with psychostimulants after PSD presented a late rebound (on the second night subsequent to the injection) in the percentage of this phase of sleep when compared to PSD rats injected with saline (P < 0.05). In addition, the current study has produced evidence of the characteristic effect of each drug on sleep architecture. Home cage control rats injected with modafinil and methamphetamine showed a reduction in SWS compared with the saline group. Methamphetamine affected sleep patterns most, since it significantly reduced paradoxical sleep, SWS and sleep efficiency before and after PSD compared to control (P < 0.05). Cocaine was the psychostimulant causing the least changes in sleep pattern in relation to those observed after saline injection. Therefore, our results suggest that abuse of these psychostimulants in a PSD paradigm aggravates their impact on sleep patterns.

INTRODUCTION

Despite the side effects of psychostimulant drugs (PD) in medical and psychiatric co-morbidity, illicit PD are broadly disseminated as an aid used by shift workers to counter discomfort in their schedules. PD lead to various physiologic effects, including hormonal (1), behavioral (2,3) and neurochemical (4) changes. Nevertheless, the problems most frequently reported by PD users are sleep disturbances (5).

PD have acute and chronic effects on sleep architecture. Difficulty in initiating and maintaining sleep as well as lower sleep efficiency (SE) and significant sleep onset delay are common amongst cocaine users (6). Further-

more, in cocaine-dependent individuals, alterations in objective sleep quality accompany their characteristic binge-abstinence cycle (7). PD abusers often have increased propensity for rapid eye movement (REM) sleep during periods of acute and subacute withdrawal from cocaine and amphetamine (8). Indeed, studies on these signs and symptoms have reported that they may reflect a state of relative functional dopamine (DA) depletion in the brain during abstinence (8).

A recent study using microdialysis coupled with electrophysiologic recordings reported an increase in DA concentration during wakefulness and paradoxical sleep (PS) compared to that during slow wave sleep (SWS) (9).

Also reported was an increased neural activity of ventral tegmental area neurons during PS (10) and a recent study showed that mice with profound DA depletion display a complete suppression of REM sleep (4). Indeed, paradoxical sleep deprivation (PSD) appears to enhance DA concentrations and DA receptor sensitivity (11,12) and these alterations may be attributable to DA postsynaptic receptor supersensitivity (11,13) and DA transporter (DAT) subsensitivity (11,14). The recovery period after PSD is marked by an increased pressure of REM sleep (15) and plays a role in restoring the function of the catecholaminergic system (16).

PD abuse often occurs within a PSD scenario, the main effect of these drugs being on the dopaminergic system (17). Internationally, amphetamine-type stimulants and cocaine are among the three most common substances of abuse (18).

Cocaine primarily inhibits DAT (19) by causing a marked increase in the synaptic cleft of striatal DA concentrations. Amphetamines are far more effective in binding DAT than cocaine, promoting a greater DA release (20). Amphetamines release DA only in cells that express DAT (21); however, the release is greater for cells that co-express vesicular monoamine transporter (VMAT). This indicates that both plasmalemmal and vesicular components are involved in the DA-releasing action of amphetamines, VMAT sequesters intraneuronal DA into vesicles for storage and subsequent release, and thus is an important regulator of cytolasmic DA concentrations and dopaminergic function. Cells that co-express DAT and VMAT have a higher capacity to retain accumulated DA by means of their vesicles, whereas the cytoplasmic pool of DA, the only one present in DAT cells, is more easily washed out by superfusion (22). The larger absolute amount of DA released by amphetamine from DAT/VMAT cells compared with DAT cells may be due to direct mobilization of VMAT and/or exchange diffusion from a cytoplasmic pool that is, to a certain extent, fed by DA leaking out of the vesicles and is therefore not as easily exhausted as in DAT cells (22).

Due to the undesired behavioral and cognitive effects observed after the use of psychostimulants like cocaine and methamphetamine, an alternative non-illicit drug that promotes wakefulness named modafinil has been approved by the Food and Drug Administration. This drug has been largely used to treat excessive daytime sleepiness and is characterized by not causing rebound hypersomnolence (23). Pharmacological evidence is unclear, but some investigators suggest that modafinil acts through competitive binding to DAT (24) and provokes a surge of extracellular DA concentration (17,25). Although dopaminergic transmission is an attractive therapeutic approach, there is considerable pharmacological evidence that modafinil acts through noradrenergic mechanisms to promote wakefulness (26,27).

Since PSD plays a crucial role in the dopaminergic system, and substances that increase the release of DA are commonly psychostimulants, the aim of the present study was to compare the sleep patterns of rats challenged with different wake-promoting drugs subsequent to 96 h of PSD.

MATERIAL AND METHODS
Animals

Three-month-old male Wistar rats bred in our facilities (~300 g) were used in this experimental protocol. The animals were maintained at 22 ± 1°C on a 12/12-h light/dark cycle (lights on at 7:00 am), with free access to food and water. The research protocol was approved by the local UNIFESP Ethics Committee (CEP No. 482/02).

Surgical preparation

The rats were anesthetized with ketamine hydrochloride and diazepam (90 and 4.5 mg/kg body weight, *ip*). After full induction of anesthesia, the animals were mounted in a stereotaxic frame and their body temperature was maintained at 36.5-37°C with a homeothermic blanket. To record the cortical electrocorticogram (ECoG), two pairs of screw electrodes were inserted through the skull ipsilaterally: 1 mm posterior to the bregma, 3 mm lateral to the central suture, and 1 mm anterior to lambda, 4 mm lateral to the central suture. Electromyogram (EMG) electrodes were implanted in the neck muscles, soldered to a 6-pin socket and covered with dental acrylic cement. After surgery, the rats were individually placed in transparent plastic cages and allowed a 14-day period of recovery from surgery comprising 10 days without the recording cable followed by a 3-day adaptation period with the polysomnography cable connected.

Sleep recording

Electrophysiological signals were recorded on a digital polygraph (Neurofax QP 223 A® Nihon Kohden, Tokyo, Japan) at a sampling rate of 200 Hz. Recordings were visually scored for 30-s epochs according to classical sleep-waking criteria as reflected either in i) the waking state, which is characterized by low voltage, fast ECoG and high EMG activity; ii) SWS, characterized by continuous high amplitude, slow ECoG activity and low EMG activity, or iii) PS, characterized by high ECoG activity and absence of EMG activity. Each 30-s epoch was defined by the wave pattern (waking state, SWS, PS), which occupied more than 50% of the time. When artifacts or noise did not allow characterization of an epoch, assessments were made based on immediate surrounding epochs. Animals

were habituated to the recording system before the rebound recording was performed.

Paradoxical sleep deprivation

The PSD method consists of placing 10 animals inside a tiled tank (123 x 44 x 44 cm) containing 14 narrow circular platforms (6.5 cm in diameter) filled with water to within 1 cm of the upper surface of the platform. Such arrangement allows the animals to move around by leaping from one platform to another. One tank was used for each group. In this procedure when an animal reaches PS, the accompanying muscle atonia causes it to touch the water and wake up. Under these conditions, the procedure causes a complete loss of PS on each of the 4 days (27). Food and water were provided *ad libitum* by placing chow pellets and water bottles on a grid located on the top of the tank. The water in the tank was changed daily throughout the 96-h period of PSD.

Groups

After the PSD period, the rats were randomly distributed into 8 experimental groups of 10 animals each: saline (SAL) home cage and PSD, cocaine (COC, 7 mg/kg, *ip*) home cage and PSD, methamphetamine (METH, 7 mg/kg, *ip*) home cage and PSD, or modafinil (MOD, 100 mg/kg, *ip*) home cage and PSD (as depicted in Figure 1).

Drugs

The doses of each drug were chosen on the basis of previous studies and prepared immediately prior to testing by dissolving in distilled water. Systemic injections were administered *ip* in a volume of 1 mL/kg: METH (7 mg/kg, *ip*) (28), COC (7 mg/kg, *ip*; Sigma, St. Louis, MO, USA) (2), and MOD (100 mg/kg, *ip*; Laboratoire L. Lafon, France) (29).

Statistical analysis

Two-way analysis of variance (ANOVA) was used to analyze group differences (treatment/sleep condition), period recordings and interaction between these two factors. For specific group comparisons, the *post hoc* Duncan test was performed and values are reported as means ± SEM, with the level of significance set at $P < 0.05$.

RESULTS
Effects of drug treatment on basal sleep values

Sleep efficiency. Light period: ANOVA revealed a significant effect of group ($F_{(7,61)} = 24.51$; $P < 0.01$), time-points ($F_{(1,61)} = 11.45$; $P < 0.01$) and an interaction effect between these factors ($F_{(7,61)} = 25.74$; $P < 0.01$). Rats injected with METH presented lower percentages of SE on the first day of recording (D1) than rats injected with SAL,

COC, and MOD ($P < 0.01$). On the second day of recording (D2), METH rats showed a significant increase in the percentages of SE compared with MOD animals ($P < 0.01$). The administration of MOD resulted in a statistical decrease of SE in relation to the SAL and COC groups at D2 ($P < 0.01$; Figure 2). *Dark period*: Statistically significant differences were detected for groups ($F_{(7,61)} = 24.51$; $P < 0.01$) and time points ($F_{(1,61)} = 11.45$; $P < 0.01$) as was an interaction effect between these factors ($F_{(7,61)} = 25.74$; $P < 0.01$). *Post hoc* analysis revealed a significant increase of SE in the METH group compared to SAL, COC ($P < 0.05$), and MOD ($P < 0.01$ on day 1) at both D1 and D2.

Slow wave sleep. Light period: Statistically significant differences were detected for group ($F_{(7,61)} = 24.51$; $P < 0.01$) and time points ($F_{(1,61)} = 11.45$; $P < 0.01$) and an interaction effect between these factors ($F_{(7,61)} = 25.74$; $P < 0.01$) was verified. Acute administration of METH induced a significant decrease in SWS compared with the SAL, COC, and MOD groups ($P < 0.01$) at D1. In contrast, at D2, rats injected with METH presented higher percentages of SWS compared with MOD rats ($P < 0.05$). The acute administration of MOD induced an increase of SWS compared with the SAL group and a decrease when compared with COC rats at D2 ($P < 0.05$), as shown in Figure 2. *Dark period*: Statistically significant differences were detected in groups ($F_{(7,61)} = 24.51$; $P < 0.01$) and time points ($F_{(1,61)} =$
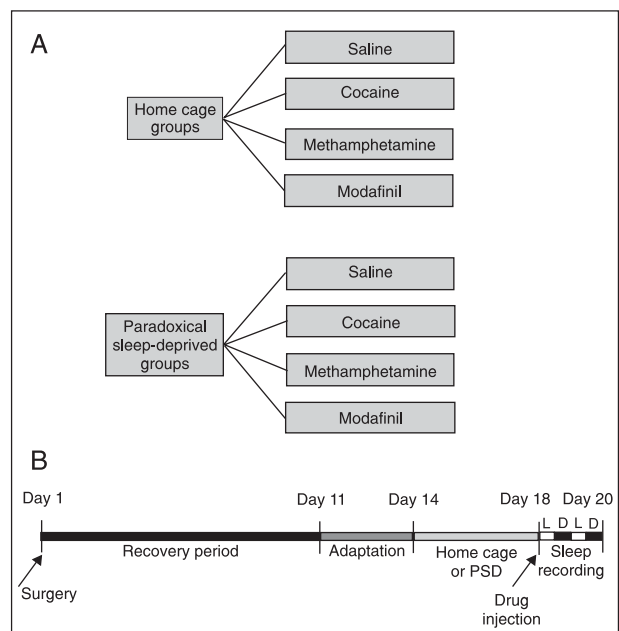
Figure 1. Schematic representation of the groups studied (panel A) and the protocol (panel B). Each group contained 10 rats which received saline, cocaine (7 mg/kg, *ip*), methamphetamine (7 mg/kg, *ip*), or modafinil (100 mg/kg, *ip*). L = light period; D = dark period; PSD = paradoxical sleep-deprived rats.
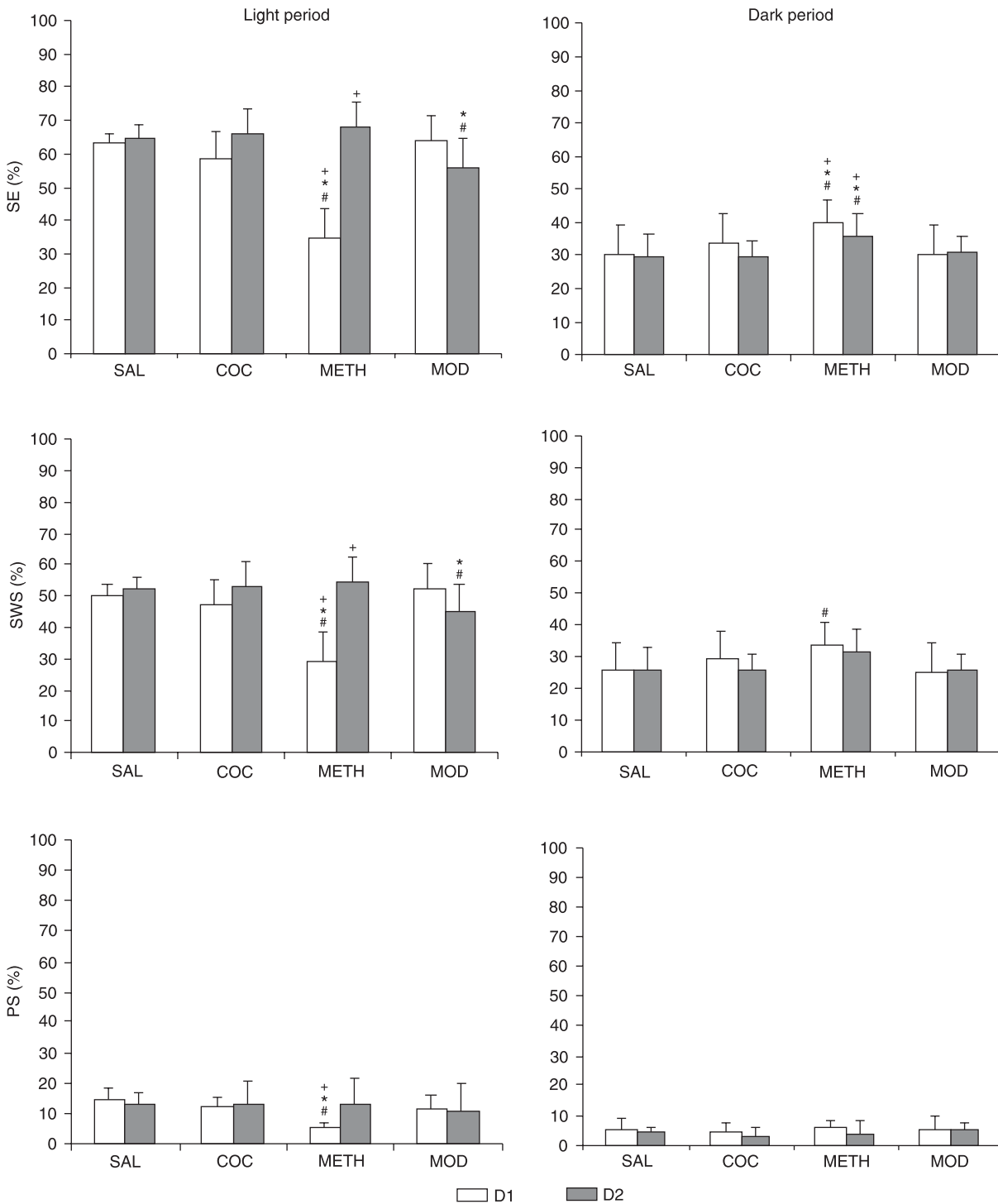
Figure 2. Percentage of each sleep parameter (sleep efficiency, SE; slow wave sleep, SWS, and paradoxical sleep, PS) observed during the light (left panels) and dark periods (right panels) in home cage rats challenged with saline (SAL), cocaine (COC, 7 mg/kg, *ip*), methamphetamine (METH, 7 mg/kg, *ip*) and modafinil (MOD, 100 mg/kg, *ip*) during two days of recording (D1 = open column and D2 = filled column). Data are reported as means ± SEM. #P < 0.05 compared to the saline group; *P < 0.05 compared to the group challenged with cocaine; +P < 0.05 compared to the group challenged with modafinil (ANOVA followed by the Duncan test).

11.45; P < 0.01). During the dark period, METH increased SWS when compared to the SAL group (P < 0.01) at D1. No statistically significant differences were observed in the remaining non-PSD groups (Figure 2).

Paradoxical sleep. Light period: As shown in Figure 2, the main effect of group ($F_{(7,61)}$ = 39.6; P < 0.01), time points ($F_{(1,61)}$ = 75.74; P < 0.01) and interaction between group and rebound recordings ($F_{(7,61)}$ = 36.44; P < 0.01) were observed. Rats injected with METH had lower percentages of PS at D1 when compared with all other groups (P < 0.05). *Dark period*: There were no statistically significant differences in the dark period.

Effects of drug challenge after paradoxical sleep deprivation

Saline. Light period: In the PSD group SE was significantly higher and SWS lower on the first day of rebound (R1) when compared with the non-PSD group recordings (P < 0.01). Regarding SWS, the percentages of this stage were significantly higher on the second day of rebound (R2) in relation to R1 for the PSD group. PSD resulted in a marked increase of PS at R1 (P < 0.01) that persisted until R2 in SAL-injected rats (P < 0.01), as shown in Figure 3. *Dark period*: The Duncan test showed that, after PSD, rats injected with SAL presented increased percentages of SE, SWS and PS compared to the non-PSD group at D1 (P < 0.01). However, at R2, these percentages were not different from control and were significantly lower than R1 (P < 0.05).

Cocaine. Light period: After PSD, rats injected with COC presented a significant increase of SE at R1 when compared with the non-PSD group (P < 0.01). The percentages of SWS at D2/R2 were significantly higher than at D1/R1 in both the PSD and non-PSD groups (P < 0.05). PSD resulted in a marked increase of PS at R1 (P < 0.01) that persisted until R2 in COC-injected rats (P < 0.01), as shown in Figure 3. *Dark period*: The Duncan test showed that, after PSD, rats injected with COC presented increased percentages of SE and PS compared to the non-PSD group at R1 and R2 (P < 0.01). However, at R2, these percentages were significantly lower than at R1 (P < 0.05).

Methamphetamine. Light period: The Duncan test revealed that METH was the only drug that promoted significant differences between D1 and D2 in SE, SWS and PS in the non-PSD groups (P < 0.01). After PSD, rats injected with METH presented a decrease in SWS at R1 that persisted until R2 compared with the non-PSD group (P < 0.01). However, when these days were compared, R2 was found to be significantly higher than R1. Indeed, this drug promoted an increase of PS at R1 when compared with the non-PSD group (P < 0.01). *Dark period*: After PSD, rats

presented increased percentages of SE compared to the non-PSD group at R1 (P < 0.01). At R2, the percentages of SE and PS were significantly lower at R2 compared with R1 (P < 0.05), as shown in Figure 3.

Modafinil. Light period: After the administration of MOD, SE and SWS were significantly reduced at R2 when compared to R1 in non-PSD rats (P < 0.05). After PSD, SE and PS were significantly higher at R1 and R2 when compared with the respective non-PSD group recordings (P < 0.01). PSD rats presented less PS at R2 compared with R1 (P < 0.05). PSD promoted an initial decrease of the SWS phase at R1 and an increase at R2 compared with the non-PSD group (P < 0.05). In this sleep stage, PSD rats presented higher percentages at R2 compared with R1, as shown in Figure 3. *Dark period*: The Duncan test showed that, after PSD, rats injected with MOD presented increased percentages of SE, SWS and PS compared to the non-PSD group at R1 and R2 (P < 0.01). The percentages of SE and PS were significantly lower at R2 than at R1 (P < 0.05).

Comparisons among psychostimulant drugs after paradoxical sleep deprivation

Sleep efficiency. Light period: The PSD + METH group had significantly lower SE at both R1 and R2 compared with the SAL sleep-deprived group and with the rats challenged with COC and MOD (P < 0.01), as shown in Figure 4. *Dark period*: At R1, METH resulted in a statistical increase in SE in PSD rats compared with rats challenged with MOD (P < 0.01), COC (P < 0.05) and SAL (P < 0.01). At R2, the PSD + METH group presented a significant increase in SE compared to the PSD + SAL (P < 0.01) group. On both rebound days, MOD led to a significant increase in sleep time compared to SAL-challenged rats (P < 0.01), as shown in Figure 4.

Slow wave sleep. Light period: Comparison between the PSD groups indicated that on the first day after sleep deprivation PSD + METH produced significantly less SWS than PSD + SAL, PSD + COC and PSD + MOD (P < 0.01). At R2, rats injected with METH presented lower percentages of SWS compared with rats injected with COC (P < 0.05). Indeed, the acute administration of MOD induced an increase of SWS compared with the SAL group at R1 (P < 0.05), as shown in Figure 4. *Dark period*: Rats injected with COC (P < 0.05), METH (P < 0.01) and MOD (P < 0.01) had more SWS compared with PSD + SAL rats at R2 (P < 0.01).

Paradoxical sleep. Light period: After PSD, rats injected with COC, METH and MOD presented a significant reduction of PS compared to SAL, and this reduction persisted until the second day in the METH group (P < 0.01). The Duncan test showed that at R1 this sleep stage was significantly reduced in the MOD-challenged group
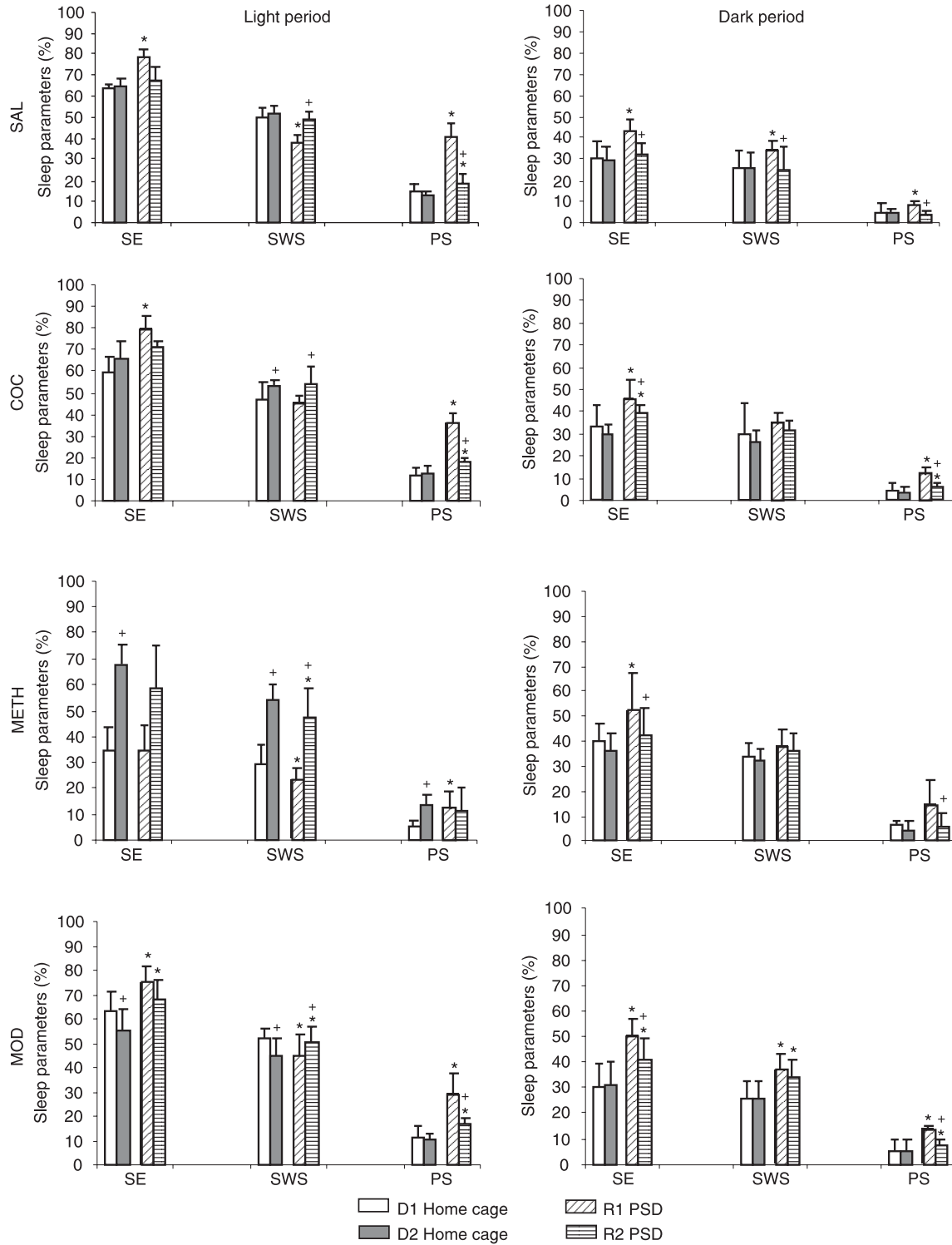
Figure 3. Percentage of each sleep parameter (sleep efficiency, SE; slow wave sleep, SWS, and paradoxical sleep, PS) observed during the light (left panels) and dark (right panels) periods in home cage and paradoxical sleep-deprived (PSD) rats challenged with saline (SAL), cocaine (COC, 7 mg/kg, *ip*), methamphetamine (METH, 7 mg/kg, *ip*), and modafinil (MOD, 100 mg/kg, *ip*) during 2 days of recording (home cage group-D1/D2; PSD group-R1/R2). Data are reported as means ± SEM. [+]P < 0.05 compared to the first day of sleep recording; *P < 0.05 compared to the non-sleep-deprived group (ANOVA followed by the Duncan test).

when compared with the PSD + COC group (P < 0.05). Indeed, in both R1 and R2, PSD + METH differed from PSD + COC and PSD + MOD (P < 0.01). The reduction was due to the lower number of PS episodes in these groups

compared to the others (P < 0.01; data not shown). *Dark period*: The groups challenged with psychostimulants presented an increase of PS compared to the PSD + SAL at R1 (P < 0.01) and this increase was observed even at R2
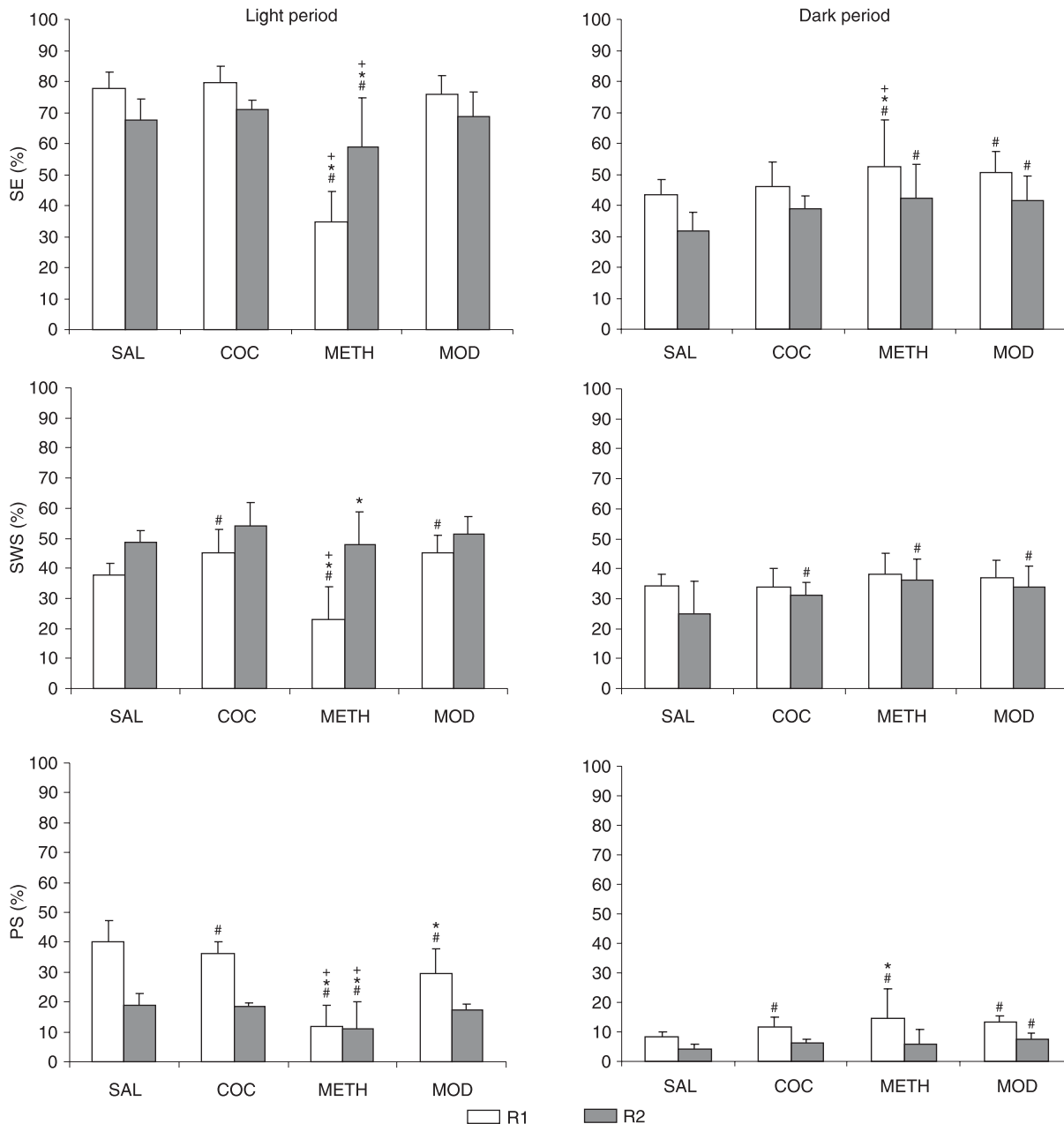
Figure 4. Percentage of each sleep parameter (sleep efficiency, SE; slow wave sleep, SWS, and paradoxical sleep, PS) during the light (left panels) and dark (right panels) periods in paradoxical sleep-deprived rats (PSD) challenged with saline (SAL), cocaine (COC, 7 mg/kg, *ip*), methamphetamine (METH, 7 mg/kg, *ip*) and modafinil (MOD, 100 mg/kg, *ip*) during two days of recording of PSD recovery (R1/R2). Data are reported as means ± SEM. #Different from the group challenged with saline; *different from the group challenged with cocaine; +different from the group challenged with modafinil (ANOVA followed by Duncan test, see text for P values).

after MOD administration. Indeed, at R1, rats injected with METH presented more PS that those injected with COC (P < 0.05), as shown in Figure 4.

DISCUSSION

The psychostimulants investigated in the current study induced different patterns of sleep-wake cycle alterations due to the effect of the drugs themselves and to their association with PSD. Our results show that immediately after 96 h of PSD, rats injected with psychostimulants presented lower percentages of PS when compared to those injected with SAL solution but, regarding SWS, after PSD rats injected with the three drugs showed a late rebound (on the second night after the injection) when compared to PSD + SAL rats. Among the drugs investigated, METH was the one that most affected sleep patterns since it significantly reduced PS, SWS and SE before and after PSD when compared with the respective SAL groups during the light period. Indeed, the four groups presented a significant increase in PS after PSD, but METH was the only drug capable of inhibiting PS rebound on the second day after administration.

Psychostimulant drugs such as amphetamines or cocaine, which facilitate catecholamine release and/or block their uptake, are commonly used for psychostimulation. D_1 and D_2 DA receptors are clearly implicated in the induction of hyperarousal (30) and it has been suggested that presynaptic activation of DA transmission is a key pharmacologic property mediating the wake-promoting effects of stimulants (31). The immediate reduction in the percentage of PS observed subsequent to the injection of METH, COC and MOD when compared to the PSD + SAL group may have been due to a complex relationship between brain dopaminergic and noradrenergic signaling systems: DA is the precursor of noradrenaline and could be a synergic ligand and a substrate for noradrenergic receptors (32). Interactions between these systems have hampered attempts to elucidate the exact target for the effects of stimulant drugs. Like PS, psychostimulants are characterized by their property of increasing mesolimbic DA neurons (9). Accordingly, rats submitted to PSD for 96 h presented supersensitivity of the postsynaptic D_2 receptor (13) and subsensitivity of the presynaptic DAT (14).

The neurotransmitter alterations observed after PSD suggest that the loss of PS reduces the release of DA by neurons. The present data show that rats injected with psychostimulants after PSD presented less PS immediately after the administration of the drugs when compared to rats injected with SAL solution, and this was most likely due to the stimulating effects of the drugs. However, during the subsequent dark period, rats injected with COC, METH

and MOD presented increased PS compared to the SAL group. These results suggest that, although the rat is more active during the dark period, the excess DA released after administration of the psychostimulants could have caused a late increase of PS in the drug groups in relation to the vehicle group. If PSD promotes neurotransmitter changes that enhance the psychostimulant effects, the combination of these two variables would promote a powerful wakefulness effect.

In general, PS is more sensitive than SWS to disruption by manipulation of catecholaminergic transmission (33,34). Our data show that, although acute COC and MOD administration to home cage groups had no immediate effect on SWS, the PSD groups presented a significant increase in SWS percentages compared to PSD + SAL-challenged rats. Indeed, after PSD, rats in the psychostimulant groups presented longer SWS than the SAL group during the second dark period after PSD. MOD promoted an immediate reduction in SWS in relation to the respective home cage group, followed by an exacerbated stimulatory effect subsequent to PSD, whereas no changes were observed in the COC group. In contrast to these processes which are increased by psychostimulants, SWS is accompanied by a reduction of catecholamine release (35). The prolonged effects of MOD on SWS may be attributed to its long half-life and in particular to noradrenergic transmission, since noradrenaline is a relevant regulating agent for sleep-state timing (36,37).

After PSD, the METH group showed a significant reduction in SWS when compared to the other groups in the same sleep condition. In contrast, rats injected with COC and MOD presented higher percentages of SWS compared with the SAL and METH groups. Unlike the COC and MOD groups, and within just the first 12 h, the home cage and PSD groups injected with METH had a significant decrease in the light period of SWS compared with the SAL group. The reduction observed in this phase may have been due to the inactivation of the DA system by the drugs, so that the mechanism of action of a high METH dose would remain effective even after a prolonged period of PSD.

It is during the light period of SWS that rat sleep becomes concentrated and a rebound period of this sleep phase was observed during the subsequent dark and light periods. On the basis of these results, we suggest that the modulation of the sleep-wake response could depend on the monoaminergic system, mainly if the dopaminergic system is involved. Since the alterations in dopaminergic pathways resulting from PSD are mainly marked by increased D_1 (38) and D_2 (14) receptors and reduced DAT (responsible for the release and reuptake of DA from within

the synaptic cleft) the most likely scenario is that dopaminergic drugs that lead to the release of DA, such as amphetamine, entail an increase in DA availability after PSD.

Recently, our group published that the PSD method applied in the present study completely abolishes PS during the deprivation period (39). After 96 h of PSD, both female (Antunes IB, Andersen ML, Baracat EC, Tufik S, unpublished results) and male (39) rats presented significantly increased PS percentages. Our data corroborate with these previous studies showing that all groups presented rebound of PS after PSD. Indeed, the group injected with METH was the only where loss of PS did not persist until R2, suggesting that this psychostimulant exerts marked long-term effects in sleep patterns. SE observed during the second dark period was significantly lower than during the first, indicating a normalized sleep pattern. After 96 h of PSD, the COC and MOD challenge caused a significant reduction in PS compared with the PSD + SAL group which may have been due to the modulation of pharmacological interaction since the sleep-wake cycle needs more time to regulate the equilibrium of basal sleep.

Our findings demonstrate that the different pharmacological profiles of COC, METH and MOD lead to sleep rebound after PSD. Overall, although the precise mechanisms underlying sleep rebound remain obscure, our data suggest that its function is to enhance sleep recovery by restoring the physiological and functional concentrations of catecholaminergic neurons.

ACKNOWLEDGMENTS

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