

Paradoxical Sleep Deprivation Influences Sexual Behavior in Female Rats

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ABSTRACT

Introduction. Sleep disturbances are a frequent complaint in women and are often attributed to hormonal fluctuations during the menstrual cycle. Rodents have been used as models to examine the effects of sleep deprivation on hormonal and behavioral changes. Among the many comorbidities common to sleep disorders, sexual behavior remains the least well studied.

Aim. To determine whether paradoxical sleep deprivation (PSD) can affect sexual receptivity (male acceptance) and proceptivity (male solicitation) behaviors in female rats.

Methods. Female Wistar rats were subjected to PSD or were maintained as controls. After this period, the estrous cycle (proestrus, estrus, and diestrus) was determined, and all females were placed with a sexually experienced male. In order to investigate the role of hormones in sexual behavior, we included additional groups that were artificially induced to be sexually receptive via administration of a combination of estradiol and progesterone.

Main Outcome Measurements. Receptivity and proceptivity behaviors, as well as progesterone and corticosterone concentrations were monitored.

Results. Selective sleep loss caused a significant increase in proceptivity and receptivity behaviors in females exclusively during the proestrus phase. The rejection response was increased in PSD rats during the estrus and diestrus phases, as compared with PSD-receptive and proestrus females. PSD reduced progesterone levels during the proestrus phase relative to the respective control group during the same phase of the estrous cycle. The PSD-proestrus females that displayed the most robust sexual response exhibited greater concentrations of corticosterone than PSD-diestrus females, with an absence of sexual solicitation behaviors.

Conclusions. PSD produced a distinct response in the hormonal profile that was consistent with the phase of the estrous cycle. These results show that sleep loss can affect sexual motivation and might lead to important clinical implications, including alterations in female physiology and reproductive abnormalities. **Andersen ML, Alvarenga TAF, Guindalini C, Perry JC, Silva A, Zager A, and Tufik S. Paradoxical sleep deprivation influences sexual behavior in female rats. J Sex Med 2009;6:2162–2172.**

Key Words. Sleep; Sleep Deprivation; Sexual Behavior; Receptivity; Proceptivity; Progesterone; Cortisol; Corticosterone; Female Rats

Introduction

Recently, Meston and Buss [1] published a comprehensive investigation regarding the

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reasons why people engage in sexual intercourse. Several evolution-based theories have suggested that men are motivated by a desire for sexual variety [2]. In contrast, women are more motivated by emotional reasons [3]. Several findings support the hypothesis that marked hormonal oscillations during the menstrual cycle function as key factors

in the sexual motivational response of females (for a review, see Wallen and Zehr [4]). However, the extent to which hormones influence female sexual behavior depends on whether motivation is an important determinant of the sexual response [5].

In addition to sexual behavior, variations in hormonal concentrations during the menstrual or estrous cycle have been associated with changes in sleep patterns [6–8]. Indeed, sleep disturbances are a frequent complaint in women [9–12]. Sleep surveys have shown that women report considerably more sleep problems than men [9,12], along with a higher occurrence of insomnia [13,14]. Moreover, abnormal menstrual cycles have been associated with sleep difficulties [7,15], and premenstrual symptoms or secondary insomnia often occur at the onset of menses [16]. Certain women may live in a constant state of sleep restriction (e.g., shift workers), and this may have a dramatic impact on multiple physiological processes.

Sleep deprivation may modulate hormone release and sexual behavior through alterations in a hormonal-neurochemical mechanism. By investigating the effects of sleep deprivation in rats, Andersen and coworkers demonstrated the facilitatory effect of paradoxical sleep deprivation (PSD) on erection and ejaculation [17,18]. Additionally, PSD influences rodent hormone profiles, particularly by increasing progesterone and corticosterone in males [19] and by reducing estrogen in diestrus-phase females [20,21]. These findings suggest that the PSD model is a reliable tool for measuring physiological responses [22–24].

Both progesterone and estradiol influence the expression of female sexual behavior in rats (typically operationalized as lordosis [25,26]). Estrogen administered alone or in conjunction with progesterone to the ventral medial hypothalamus promotes lordosis in rats [27]. However, the proportion of rats displaying lordosis and its intensity are increased when progesterone is concurrently administered to the ventral tegmental area [28]. Progesterone also reduces rejection behavior [29,30]. Estrogen, in turn, induces a coordinated peripheral genital swelling and lubrication response, increasing clitoral and vaginal blood flow, among other effects [31].

Interestingly, the distinction between the ability to copulate and the desire to copulate has been reported to be based on female sexual initiation, as the latter is the only valid indicator of female sexual motivation [32]. Recently, Bullivant et al. [33] reported that women were more sexually active on days prior to and during the preovulatory

surge. This pattern was evident only when women initiated sexual activity, indicating an increase in women's sexual motivation rather than improved attractiveness. Therefore, investigations of the potential hormonal mechanisms underlying sexual motivation in different contexts may provide important information regarding questions about sexual activity and the menstrual cycle.

Since most adults have experienced sleep deprivation at some stage of their lives, research using preclinical models can provide a framework to determine how sleep loss might affect female sexual behavior. We previously demonstrated that sleep deprivation disrupts the estrous cycle in rats by influencing hormonal profiles, and that stress (a factor that is associated with sleep loss) has a suppressive effect on the hypothalamic-pituitary-gonadal axis. Accordingly, we hypothesized that female rats deprived of sleep would present a reduced sexual response because of the altered release of progesterone. To the best of our knowledge, this is the first study to investigate whether paradoxical sleep deprivation can affect receptivity (acceptance) and proceptivity (solicitation) behaviors in female rats. We also examined a possible hormonal basis for such behaviors in female rats exposed to PSD.

Methods

Subjects

Male and sexually inexperienced female Wistar rats (2.5 to 3 months of age) from the animal facility of the Institute of Pharmacology at the Universidade Federal de Sao Paulo were housed in standard polypropylene cages on a 12:12 hours light-dark cycle (lights on at 6:00 AM) at 22°C. Rat chow and water were provided ad libitum. The rodents used in this study were maintained and treated in accordance with National Institutes of Health guidelines. All animal procedures were approved by the university's Ethics Committee (CEP1503/07-434/05).

Determination of the Estrous Phase

The reproductive cycle of female rats is called the estrous cycle. It is characterized by the existence of the following distinct stages/phases: proestrus, estrus, metestrus (or diestrus I), and diestrus (or diestrus II). Ovulation occurs from the beginning of proestrus to the end of estrus. Vaginal smear cytology was used to determine the phase of the estrous cycle, and all samples were obtained

between 3:00 PM and 5:00 PM. Smearing was conducted during the 14 days prior to the experimental period. All animals were smeared daily, and only rats that had two consecutive regular cycles were selected. Changes in vaginal epithelial cell morphology were used to indicate the phase of the estrus cycle in terms of the occurrence of the following three cell types in the vaginal smears: leukocytes, cornified cells, and nucleated epithelial cells. Proestrus was characterized by many nucleated epithelial cells and few leukocytes, estrus by many cornified cells and no leukocytes, and diestrus by the presence of few nucleated epithelial cells and many leukocytes.

Paradoxical Sleep Deprivation (PSD)

The animals were paradoxically sleep-deprived over a period of 96 hours using the modified multiple platform method. This period of PSD was selected because most genital reflexes in males [34] and hormonal alterations in the female estrous cycle [20] are produced during this time span. The selective PSD method is based on the fact that sleep deprivation in modern life occurs predominantly in the paradoxical sleep (PS)/rapid eye movement (REM) phase of sleep during the second half of the night. Five female rats at a time were placed inside a tiled water tank (58 × 48 × 20 cm), which contained eight circular platforms (6.5 cm in diameter), submerged in water up to 1 cm below their upper surface. The rats could move around inside the tank by jumping from one platform to another. When they reached the paradoxical sleep phase, muscle atonia set in, and they fell into the water and awoke. Throughout the study, the experimental room was maintained at a controlled temperature (22 ± 1°C) using a 12-hour light–dark cycle (lights on from 6:00 AM–6:00 PM). The control (CTRL) groups were maintained in their home cages in the same room as the experimental rats for the duration of the study. The CTRL group female rats displayed normal sleep patterns, as recorded by an electrocorticogram [8]. Food and water were provided ad libitum by placing chow pellets and water bottles on a grid located at the top of the tank. The tank water was changed daily throughout the PSD period.

Groups

In the present study, naturally cycling and artificially hormone-enhanced (receptive-R) female rats were used. After 96 hours of PSD or an equivalent period in the home cage (CTRL) groups, the estrous cycle was determined, and

female rats were distributed into the groups described below. No animal received more than one experimental treatment.

1. CTRL-D: Control rats maintained in the home-cage and tested during the diestrus phase (N = 12).
2. PSD-D: Rats subjected to 96 hours of PSD and tested during the diestrus phase (N = 11).
3. CTRL-E: Control rats maintained in the home-cage and tested during the estrus phase (N = 12).
4. PSD-E: Rats subjected to 96 hours of PSD and tested during the estrus phase (N = 12).
5. CTRL-P: Control rats maintained in the home-cage and tested during the proestrus phase (N = 8).
6. PSD-P: Rats subjected to 96 hours of PSD and tested during the proestrus phase (N = 8).
7. CTRL-R: Control rats maintained in the home-cage and treated with estradiol + progesterone prior to the sexual behavior test (N = 12).
8. PSD-R: Rats subjected to 96 hours of PSD and treated with estradiol + progesterone prior to the sexual behavior test (N = 12).

Female Sexual Behavior and Experimental Design

Female rats were distributed into PSD or CTRL groups (N = 8–12/group). The vaginal smear was performed daily during the PSD period or at equivalent times for the CTRL rats. Another set of females injected with estradiol + progesterone was included to investigate the effect of PSD on hormone-enhanced (artificially receptive) females. At the end of the PSD period, the estrous phase of the females was determined and the rats were placed in a circular plexiglass arena (55 cm in diameter and 40 cm tall) with a sexually experienced male. Behavioral observations were carried out after onset of the dark phase (2 hours after the lights had turned off) in a temperature-controlled room. In order to reduce any bias that may have been generated by the physical settings during the sleep deprivation protocol, the PSD group was placed in a dry environment for 5 minutes directly after the PSD protocol was carried out and prior to the sexual behavior observations, whereas the control rats were placed in the wet environment for the same period of time in the same room in which the males were housed. The male was allowed to mount the female 10 times or for a total interaction time of 30 minutes, whichever occurred first. The receptivity of each female was determined by the lordosis

quotient (LQ = [number of lordosis responses/10 mounts] × 100). Proceptive behaviors were measured by the frequency of solicitations (characterized by hopping, darting, and ear-wiggling). Rejection responses for each female (fighting, kicking, and prone defensiveness) were also recorded. All behavioral observations were performed by only one experienced researcher who was blinded to the treatment conditions.

Blood Sampling and Hormone Determination

After the behavioral test, the PSD and CTRL female groups were taken to an adjacent room and decapitated with minimum discomfort. The control group rats were decapitated along with the PSD groups for each estrous cycle phase. Blood was collected in glass tubes and centrifuged at 3018.4 g for 15 minutes at room temperature for serum, and at 4°C to obtain plasma. The intra-assay coefficients of variation are indicated in parentheses. Progesterone (6.5%) was measured by a competitive immunoassay (TOSOH Corporation, Tokyo, Japan), with a minimal detectable concentration of 0.1 ng/mL. Plasma corticosterone (7.1%) levels were assayed using a double antibody radioimmunoassay method specific for rats and mice using a commercial kit (MP Biomedicals, Aurora, OH, USA). The sensitivity of the assay was 0.25 ng/mL.

Hormones

All drugs were obtained from Sigma Chemical Co. (St. Louis, MO, USA). Sexual behavior was induced in females by subcutaneous injections of crystalline estradiol benzoate (10 µg/0.1 mL reagent grade sesame oil) and progesterone (500 µg/0.1 mL of sesame oil). Estradiol was injected 48 hours and 24 hours prior to testing, and progesterone was injected 4 hours before testing. The doses, routes, and latencies of administration were selected based on previous experiments to optimize the frequency of the LQ [35].

Statistical Analyses

The Fisher's exact test was used to compare the proportion of proceptive females and rejection responses [36], and statistical differences between the groups were analyzed by comparing the PSD relative to the respective CTRL during the same phase of the estrus cycle and between the separate CTRL and PSD groups. Since the distribution of the LQ values was not normal and the Bartlett test revealed an absence of homoscedasticity (unequal

variances), the data were analyzed by Kruskal-Wallis ANOVA followed by the Mann-Whitney *U* test to compare the PSD vs. the respective control group during the same phase of the estrus cycle, and separately for the control and PSD groups among the different phases. For hormonal concentrations, the PSD and control groups were compared by one-way ANOVA followed by the Duncan test for comparison between groups. The values are expressed as means ± SEM. The level of significance was set at $P < 0.05$.

Results

Behavioral Tests

Receptivity

Comparisons between the groups were performed using the Kruskal-Wallis test, followed by the Mann-Whitney *U* test. Receptive CTRL female rats showed a significant increase in lordosis compared with the CTRL-D ($P < 0.01$), CTRL-E ($P < 0.02$), and CTRL-P ($P < 0.05$) females. No significant differences were observed between the other CTRL groups. The PSD-P and PSD-R groups exhibited higher lordosis rates than PSD-D ($P < 0.001$) and PSD-E rats ($P < 0.01$). PSD enhanced receptivity behavior in proestrus female rats (Figure 1A), as indicated by the fact that females in proestrus displayed higher lordosis compared with the respective CTRL group (95% vs. 50%; $P < 0.01$). The PSD-D, PSD-E, and PSD-R groups demonstrated no significant effects compared with the respective CTRL groups. These results suggest that selective sleep deprivation involving paradoxical sleep affected receptive behavior exclusively in the proestrus phase.

Proceptivity

As shown by the Fisher's exact test in Figure 1B, the CTRL-E, CTRL-P, and CTRL-R groups demonstrated increased proceptivity behavior compared with CTRL-D rats ($P < 0.01$). No statistically significant differences were found among other estrus phases in the CTRL groups. The percentage of the PSD-P and PSD-R groups displaying behaviors such as hopping, darting, and ear-wiggling was significantly higher than that of the PSD-D ($P < 0.001$) and PSD-E ($P < 0.001$) groups. Similar to receptivity, PSD increased proceptivity behaviors with respect to the respective CTRL-P group during the proestrus phase (+66.6%; $P < 0.04$).

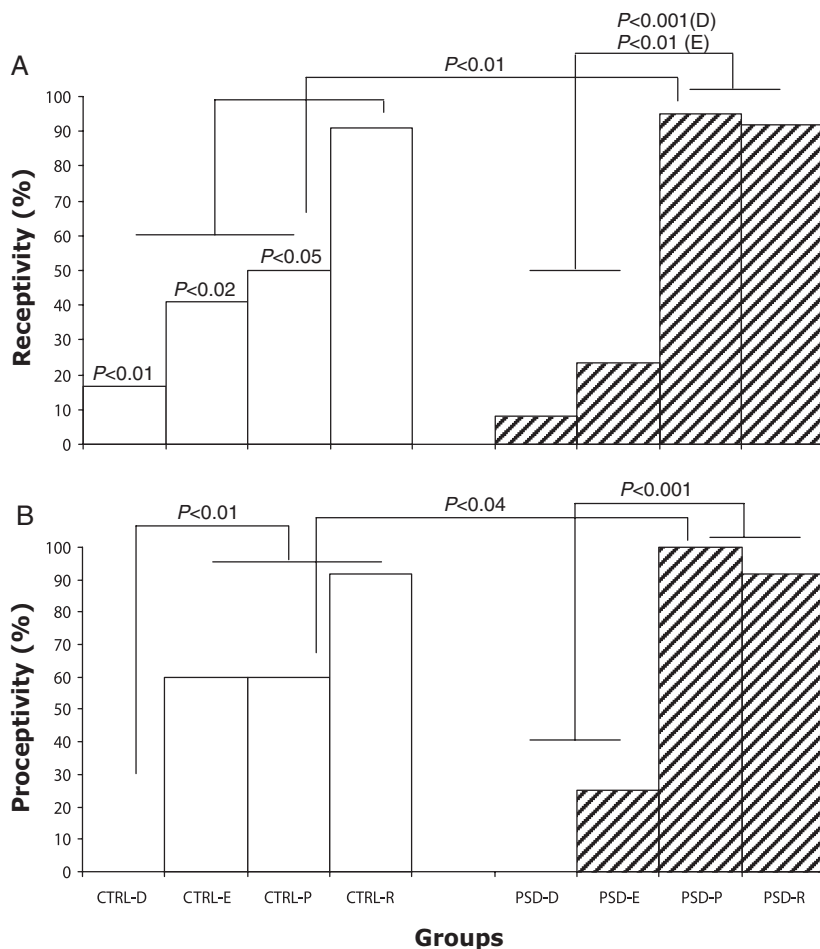


Figure 1 Percentages of female rats displaying (A) receptive and (B) proceptive behaviors in the control (CTRL) and paradoxically sleep-deprived (PSD) groups during diestrus (D), estrus (E), and proestrus (P) phases, as well as in artificially-induced receptive (R) females. Kruskal-Wallis test followed by the Mann-Whitney *U* test (receptivity) and Fisher Exact test (proceptivity) ($N = 8-12$ for each group).

Rejection Response and Latency

Rejection behaviors were not statistically different among the CTRL groups (Figure 2A). The Fisher's exact test showed that the percentages of females displaying rejection behaviors in the PSD-D and PSD-E groups were higher than the PSD-P ($P < 0.01$ and $P < 0.03$, respectively) and PSD-R groups ($P < 0.02$ and $P < 0.05$, respectively). The high percentage of PSD-D and PSD-E females displaying rejection behaviors resulted in an increased latency for the male to complete 10 mounts when paired with females in the PSD-P and PSD-R groups ($P < 0.01$). PSD females in proestrus did not show any rejection responses. The CTRL-R demonstrated decreased latency compared with the CTRL-D, CTRL-E, and CTRL-P groups ($P < 0.01$ —Figure 2B). The latency observed in the PSD-P group differed from that in the respective CTRL groups (779.8 vs. 329.7 seconds; $P < 0.04$). Thus, PSD did not influence rejection behaviors in any group, but it decreased the latency in initiating sexual behavior for females in proestrus (Figure 2B).

Hormonal Analysis

Progesterone

In the CTRL groups, one-way ANOVA followed by the Duncan test demonstrated that progesterone reached its highest concentrations in the CTRL-P and CTRL-R females compared with the CTRL-E group ($P < 0.03$ and $P < 0.01$, respectively), as shown in Figure 3A. No significant differences were observed between the CTRL-D and CTRL-E groups. Progesterone concentrations were increased in PSD-R females when compared with the PSD-E group ($P < 0.01$). The high percentage of PSD-P females displaying sexual behaviors was accompanied by a reduction in progesterone (CTRL-P vs. PSD-P, $P < 0.01$). Sleep deprivation did not significantly affect progesterone concentrations in the PSD-D, PSD-E, and PSD-R groups in comparison to the respective controls.

Corticosterone

There were no statistically significant differences in corticosterone values among the CTRL groups, as demonstrated by the ANOVA/Duncan tests.

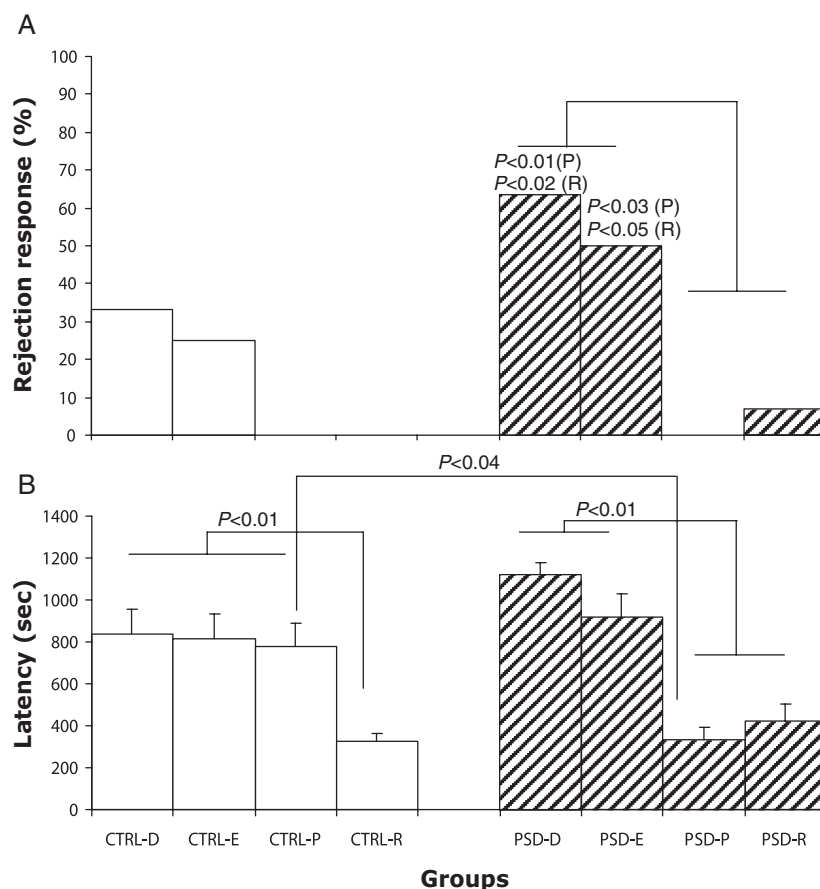


Figure 2 Percentage of female rats displaying (A) rejection behaviors and (B) latency (in seconds) for males to complete 10 mountings in control (CTRL) and paradoxically sleep-deprived (PSD) groups during diestrus (D), estrus (E), and proestrus (P) phases, as well as in artificially-induced receptive (R) females during the maximum 30 minutes test. Fisher (rejection response) and ANOVA followed by the Duncan test (latency). Data are expressed as means \pm SEM.

Corticosterone concentrations were significantly higher in the PSD-P group than in the PSD-D group ($P < 0.001$). There were no significant differences between the other PSD groups. Female rats undergoing PSD and tested during diestrus demonstrated lower corticosterone concentrations than their respective CTRL group counterparts ($P < 0.01$). No significant differences were obtained between the CTRL and PSD groups in the other estrous phases.

Discussion

The results of the present study provide evidence that sleep deprivation can affect sexual behavior in female rats. Specifically, PSD enhanced the sexual response in proestrus PSD rats, as manifested by greater adoption of the lordosis posture. Female proceptive behaviors paralleled sexual receptivity, suggesting that the females initiated and/or maintained these sexual interactions. This pattern of proceptive behavior is recognized as an important signal of sexual incentive and motivational processes, and serves as a stimulatory agent of male

sexual motivation (as observed by a reduced latency to complete ten mounts, Figure 2B). Furthermore, an absence of the rejection response was observed in this group, whereas PSD in the diestrus and estrus groups produced behaviors characterized by boxing, fighting, and prone defensiveness.

Beyond sexual behavior, the neuroendocrine changes in females remain incompletely understood. Theoretically, ovarian hormones may increase female sexual motivation via the generation of a central motive state that serves to energize behavior and sensitize the individual to sexual incentives that signal potential mating opportunities [37,38]. Many lines of evidence clearly demonstrate that progesterone is required for the female to display the complete proceptivity reproductive pattern [39,40]. However, how sleep loss or other factors such as stress modify sexual behaviors in females remains unclear. Interestingly, the proestrus group was the only group in which sleep deprivation produced a statistically significant increase in proceptive and receptive behaviors in comparison to the respective estrous phase control animals. The role of progesterone levels in reduc-

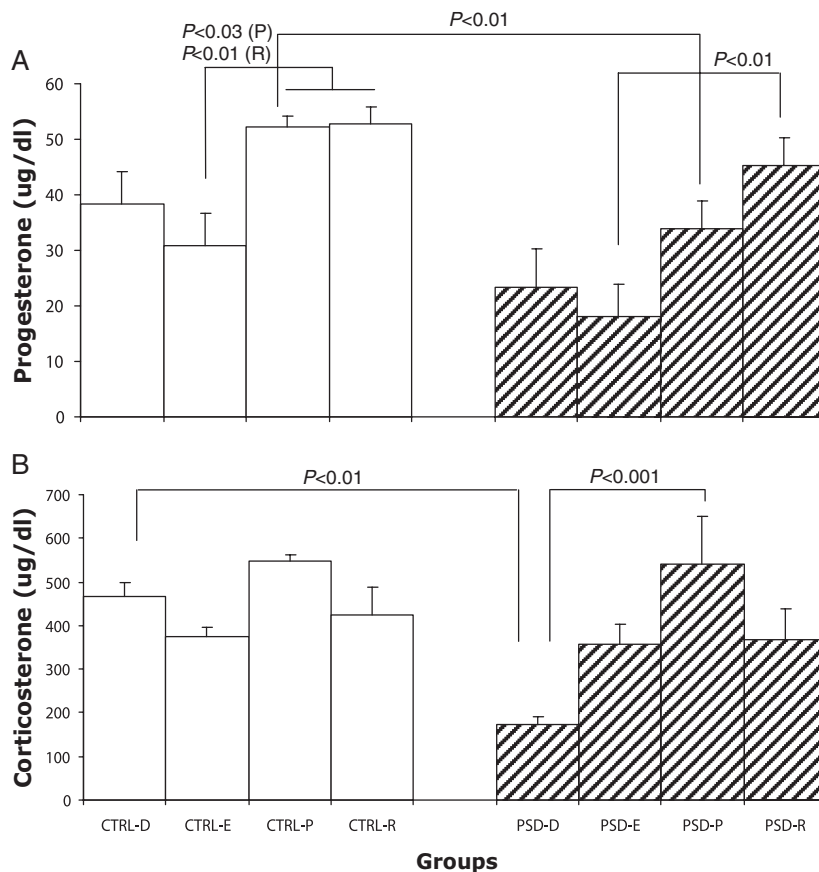


Figure 3 Serum (A) progesterone (in ng/mL) and (B) corticosterone (in ng/mL) in control (CTRL) and paradoxically sleep-deprived (PSD) females during diestrus (D), estrus (E), and proestrus (P) phases, as well as in artificially-induced receptive (R) females. *Compared with the respective control (CTRL) group; ANOVA followed by the Duncan test. Data are expressed as means \pm SEM.

ing sexual desire has been previously documented [41]. The present results corroborate these previous findings, demonstrating that reduced levels of progesterone may contribute to the increase in receptive and proceptive behaviors in the PSD-proestrus group. Moreover, PSD acted by enhancing the sexual response in those females. Thus, progesterone seemed to play a major role in the consummatory (lordosis) and appetitive (wide range of proceptive behaviors) aspects of sexual interaction in proestrus females subjected to PSD.

The intersection between female gonadal hormones and the response to stress occurs at both central and peripheral sites [42]. Several components of this hypothalamic-pituitary-adrenal (HPA) axis are also modulated by gonadal steroids [43]. Activation of the HPA axis can similarly alter reproductive function [44]. An interesting finding in the present study was the significant increase in corticosterone concentrations in the PSD-proestrus as compared with the diestrus group. The PSD-proestrus group displayed a high sexual response relative to the PSD-diestrus group, which in turn exhibited absolutely no solicitation behaviors to mate with the male and displayed the highest

increase in rejection responses. As a result of the sleep deprivation technique used in the present study, it seems reasonable to consider that a significant stress component is intrinsic to sleep loss itself. The increased corticosterone levels in the PSD females that exhibited greater sexual behavior suggested that release of glucocorticoids might be necessary to promote sexual interest under stressful conditions, since no wide fluctuation in corticosterone related to sexual behavior was observed in the control groups. Indeed, it has been reported that higher stimulated cortisol are associated with genital arousal suggesting that cortisol concentrations may be associated with sexual desire in healthy women [45]. On the other hand, recent studies have demonstrated that some women with impaired sexual function respond to sexual stimuli with an increase in cortisol, which is the opposite of the results observed in previous studies of healthy women [46–48]. In turn, Hamilton's et al. [48] reported that women whose cortisol increased after viewing erotica had lower arousal scores. Moreover, concentrations above the optimal levels have been suggested to impair sexual performance or completely inhibit sexual behavior [49].

Given that feedback related to an increased cortisol response may trigger disruptions in other hormonal mechanisms, these findings have important implications for both reproductive health and sexual function in women. As female rats deprived of sleep during proestrus showed increased sexual behaviors and higher corticosterone concentrations than during diestrus, it is possible that increased levels of stress hormone do not necessarily exert a negative effect on sexual response in females.

A previous study using the very same protocol for PSD demonstrated that the PSD-diestrus group exhibited higher concentrations of progesterone and corticosterone than the respective control rats [20]. However, that study demonstrated isolated effects of PSD on the hormonal profiles of naïve female rats. Inconsistencies with the current findings may be explained in part by the fact that the hormonal profile obtained in the present study was investigated after a sexual behavior session. In the present study, all females were exposed to male sexual behavior that is known to include a set of natural stimuli linked to stress responses [50]. Other researchers have suggested that when the environment includes sexual stimuli, the hypothalamic-pituitary-gonadal axis is activated and, consequently, the HPA axis (which is also activated) cannot inhibit a system that has been previously stimulated. Furthermore, Frye et al. [51] reported that females exposed to the presence of males demonstrated increased levels of progesterone, estradiol, and corticosterone. These findings demonstrate the complexity of studying feminine sexual behavior, as well as the obvious difficulty inherent to interpreting the results when PSD and behavioral paradigms are included.

Sleep disorders affect women differently than they affect men and may exhibit different manifestations and prevalences. Women of all ages display a higher prevalence of both sleep disturbances and insomnia than men [13]. Since insomnia and other sleep complaints have a negative impact on the quality of life and also induce comorbid disorders, it is important to address how sleep loss affects sexual behavior. Guilleminault et al. [52] demonstrated that 48% of men with sleep apnea report erectile dysfunction, ejaculatory problems, and/or diminished libido. Sleep apnea was also associated with a significant decrease in sexual function in women [53] independent of age and comorbid disease [54]. In contrast, patients with situational impotence presented a full erection after 24 hours of sleep deprivation under audiovisual stimuli [55].

To the best of our knowledge, no study has focused on the impact of PSD on the sexual behavior of females. Given that sleep deprivation disrupts the estrous cycle in female rats [20], we speculate that the sleep disturbances induced by insomnia or accumulative sleep debt may have a negative impact on the menstrual cycle. Indeed, nurses who work night shifts exhibit the shortest menstrual cycles [56], whereas women with abnormal menstrual cycles demonstrate more pronounced sleep difficulties [7]. In light of the limited understanding of the link between secretion patterns and neural-hormonal control of sexual behavior, our future directions will include experimental approaches designed to address the effects of sleep loss on the female sexual response in the context of hormonal treatments.

In summary, the present study aimed to explore the role of sleep deprivation in sexual behavior across the estrous cycle in female rats. Demanding lifestyles that are often associated with reduced sleep duration, are becoming increasingly common in modern society. Abbreviated sleep may occur as a result of a number of factors such as social life, artificial light, shift work, or sleep disturbances. Our results suggest that PSD plays an important role in modulating the physiology of sexual behavior in female rats, indicating that changes in sexual motivation induced by sleep loss might lead to marked alterations in reproductive performance. Since progesterone is necessary for ovulation, we conclude that the alterations in hormonal profiles caused by sleep deprivation may influence normal female reproductive physiology. These findings may help elucidate the connection between sleep loss and reproductive function. Our study may point toward new horizons in terms of the influence of sleep deprivation on female sexuality.

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