Effects of sleep deprivation during pregnancy on the reproductive capability of the offspring

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Objective: To investigate the effects of sleep deprivation during pregnancy on the reproductive capability of the offspring.
Design: Using a sleep loss model or control home-cage group (male and females rats) to evaluate sexual behavior and hormonal profile in males and females F1 offispring.
Setting: Laboratory.
Animals(s): First experiment: Pregnant females were exposed to sleep restriction (SR) protocol and the F1 generation was evaluated. Second experiment: male rats were submitted to SR or paradoxical sleep deprivation (PSD) protocol and the F1 generation was evaluated.
Intervention(s): Male and female rats were subjected to sleep restriction (SR) for 21 days or paradoxal sleep-deprived (PSD) for 96 hours.
Main Outcome Measure(s): Sexual behavior and hormonal levels during the adult phase were analyzed in F1 offspring of female and male rats submitted to sleep loss.
Result(s): F1 male offspring of SR females had lower motivation for sex and reduced progesterone concentrations. In contrast, F1 female offspring displayed significantly enhanced proceptivity compared with control offspring. F1 female offspring also demonstrated hypersexuality by mounting the males in the absence of any significant hormonal alterations. F1 male offspring of SR or paradoxically sleep-deprived (PSD) males presented a decline in the sexual response, accompanied by a reduction in testosterone concentrations. Proceptivity was significantly increased among F1 female offspring of PSD and SR males compared with control offspring.
Conclusion(s): SR in progenitors may alter sexual behavior of the F1 offspring in adulthood. These findings reveal far-reaching consequences of sleep deprivation, and suggest that parental sleep influences the reproductive capability of subsequent generations. (Fertil Steril® 2013;100:1752–7. ©2013 by American Society for Reproductive Medicine.)
Key Words: Sleep deprivation, pregnancy, sexual behavior, offspring, hormones, rats

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Sleeping habits of humans differ markedly from those of the pre-industrial era (1) when individuals were able to sleep longer. The reason for shortening present-day sleeping time stems from the pressure to meet the growing demands imposed by a routine of work, study, and social commitments. Current sleep restriction (SR) is compounded by other sleep disturbances, constituting an important public health issue (2, 3) with far-reaching consequences.

In nonhuman models, lack of sleep influences sexual hormones, leading to a reduction in testosterone (T) and increased concentrations of progesterone (P) and glucocorticoids in male rats (4), in addition to hampering male sexual performance (5). In female rats, the lack of sleep also modulates the release of ovarian hormones (6–8). Such effects have significant relevance considering that hormones regulate sexual function in two basic ways: first, they act over the course of development from conception to sexual maturity to produce the physiologic, anatomic, and behavioral characteristics that distinguish male from female; and second, they activate reproductive behavior in adulthood.

As described above, the present-day lifestyle is detrimental to sleep

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homeostasis and may lead to disruptions in neuroendocrine functions important for reproduction. In addition, stress has been shown to interfere in male and female reproductive capability in various animal species (9, 10), and curtailment of sleep has an inherent stress component (11). Many studies have examined the consequence of stress during pregnancy on the development of the offspring (12–15). However, none of those studies directly analyzed the effects of sleep deprivation during pregnancy. Moreover, no study has set out to understand the effects of SR in the progenitor as it relates to the sexual maturation and development of offspring. Parental influence on the development of offspring is indeed of great relevance, made evident by a study demonstrating behavioral alterations in offspring of alcohol-consuming parents (16) and the verification of the influence of paternal obesity on the offspring (17).

In view of the reduction in the rate of fertility among couples over the past decades (18) concomitant with shortening in sleep time, the present study sought to understand the effects that lack of sleep has on both the progenitor and the reproductive capability of the offspring.

METHODS

General Methods

Subjects. Adult Wistar-Hannover rats were bred and raised at the animal facility of the Centro de Desenvolvimento de Modelos Experimentais para Medicina e Biologia of the Universidade Federal de São Paulo. The animals were housed in a colony room maintained at a constant temperature of 22 ± 1°C with a 12-h light-dark cycle (lights on at 07:00), and had free access to water and food. All animals were treated in accordance with the National Institutes of Health guidelines, and all procedures were approved by the University's Ethics Committee (CEP nos. 09/071 and 09/1444).

Determination of the estrous phase. The estrous cycle 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 17:00 and 19:00. Changes in vaginal epithelial cell morphology were used to indicate the phase of the estrus cycle based on the occurrence of 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. Paradoxical sleep deprivation (PSD) was carried out for 96 hours with the use of the modified multiple-platform method. The 96 hours period was chosen because previous studies have demonstrated that the most dramatic alterations in behavior (19) and hormone concentrations (4) occur after this duration of PSD. Rats were placed, one at a time, inside a tiled water tank (143 × 41 × 30 cm) containing 14 circular platforms (each 6.5 cm in diameter) with the water level within 1 cm of the upper surface. The rats could move within the tank by jumping from one platform to another. When they reached the paradoxical phase of sleep, muscle atonia caused them to fall into the water and awaken. Throughout the study, the experimental room was maintained at a controlled temperature (22 ± 1°C) with a 12-h light-dark cycle (lights on at 07:00 and off at 19:00). The rats had free access to food and water located on a grid on top of the tank. The water in the tank was changed daily during the PSD period. All animals began their PSD period in the dark phase of the light-dark cycle (19:00) because we elected not to invert the light-dark cycle. Thus, the light-dark cycle was maintained as usual, and sexual behavior was evaluated during the dark phase.

Sleep restriction. The SR protocol was based on the technique used to achieve PSD. However, in the SR protocol rats were kept on the platforms for 18 hours (beginning at 16:00) and allowed to sleep for 6 hours (from 10:00 to 16:00) every day for 21 days, which enabled partial compensation for the sleep loss (20). The time interval 10:00–16:00 was chosen because that is when paradoxical sleep is at its highest in rats.

Male sexual behavior. The testing of sexual behavior was performed with the use of a plexiglas cylindric arena 45 cm in diameter. Dim red lights shone during the dark phase of the light-dark cycle. A male rat was introduced into the arena 5 minutes before a sexually receptive female. Sexual receptivity in the females was established by administering estradiol benzoate (10 μg in 0.1 mL sesame oil subcutaneously; Sigma Chemical Co.) 48 hours and 24 hours before testing, and P 4 hours before (500 μg in 0.1 mL sesame oil subcutaneously; Sigma Chemical Co.) (5). Each test of sexual behavior lasted 30 minutes after the introduction of the female, during which the following variables were recorded by a single experienced researcher who was blinded to the treatment conditions: time to first mount, intromission and ejaculation latencies, total number of mounts (i.e., mounts with pelvic thrusting), intromissions (mounts with pelvic thrusting and penile insertion) and ejaculations. Rates of copulation [number of intromissions/(number of mounts + number of intromissions)], inter-intromission interval (ejaculation latency/number of intromissions) and intercopulatory interval [ejaculation latency/(number of intromissions + number of mounts)] were calculated (21).

Female sexual behavior. Female rats were placed in a plexiglas cylindric arena 45 cm in diameter with a sexually experienced male. Behavioral observations were carried out after 2 hours after onset of the dark phase in a temperature-controlled room. 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 a single experienced researcher who was blinded to the treatment conditions.

Blood sampling and hormone determination. Immediately after behavioral testing, rats were taken to an adjacent room and decapitated. Blood samples were collected and stored individually. Blood was collected in glass tubes and centrifuged at 3018.4*g* for 15 minutes at room temperature and then frozen at −20°C until assayed. Serum T [intra-assay coefficient of variation (ICV) 7.7%] and P (ICV 6.5%) were measured by a chemiluminescent enzyme immunoassay (Advia Centaur; Bayer Corp.). These hormones were analyzed because our group has consistently demonstrated their role in sexual response in both male and female rats (6–8).

Experimental Design

Experiment 1: Sexual behavior and hormones in offspring of SR or CTRL females. Twenty-four sexually naive female rats and 10 sexually experienced male rats were used in this experiment. The females were ~75 days old and the males ~90 days old at the beginning of the protocol. All offspring produced were observed for the behavioral tests. Rats were placed together to allow copulation; copulation occurred during the dark phase in a cage containing one receptive female (at the end of the proestrus phase to the beginning of the estrus phase) and one of the sexually experienced males. The presence of the vaginal plug and the identification of spermatozoids in the vaginal smear confirmed copulation, ejaculation, and pregnancy. Throughout pregnancy (21 days) the females were either kept individually in their home cages (CTRL) or underwent SR for the duration of their pregnancy. Because poor sleep quality occurs in pregnant women throughout the gestational period, in this experiment we chose to submit the rats only to the SR, and not the PSD, protocol to better mimic conditions in humans. Ninety days after birth, male (n = 25 each group) and female (n = 24 CTRL; n = 28 SR) F1 offspring underwent sexual behavioral tests.

Experiment 2: Sexual behavior and hormones in offspring of CTRL, PSD, or SR males. Because sexually inexperienced male rats may display low performance, we followed an established protocol that standardizes the degree of copulatory activity and avoids possible bias (22). Twenty-four hours after the last training session, the rats with excellent sexual performance were selected and subjected to PSD for 96 hours or SR for 21 days, or maintained in the home cage as a CTRL group. Immediately after this period, the males underwent the copulatory session. Each male was placed, during the dark phase, in a cage containing one receptive female (at the end of the proestrus phase to the beginning of the estrus phase). Throughout pregnancy (21 days) the females were kept individually in their home cages. Ninety days after birth, male (n = 37 CTRL; n = 45 PSD/SR) and female (n = 31 CTRL; n = 33 PSD; n = 28 SR) F1 offspring underwent sexual behavioral tests.

Statistical Analyses

Fisher exact test was used to analyze the parameters of sexual behavior in the female rats. The Mann-Whitney test was used to analyze the males' sexual parameters in the first experiment (2 groups: CTRL and SR) and the Kruskal-Wallis test followed by the Mann-Whitney test in the second experiment (3 groups: CTRL, PSD, and SR). Regarding the hormonal concentrations, the groups were compared by one-way analysis of variance followed by the Duncan test. The values are expressed as mean ± SEM. The level of significance was set at $P<.05$.

RESULTS

Experiment 1: Sexual Behavior and Hormones in Offspring of CTRL or SR females

Male offspring. F1 male offspring of females who underwent SR throughout pregnancy displayed longer latency to the first mount ($P<.008$; Table 1), as well as a reduced number of mounts within the 30-minute period of observation ($P<.01$; Table 1), findings that clearly indicate compromised sexual motivation. However, intromission latency, ejaculation latency, and total number of intromissions and ejaculations were unaffected, indicating unaltered sexual performance. F1 males from SR parental females had significantly lower P concentrations compared with F1 males from CTRL parental females ($P<.05$; Table 2), and T remained unaltered between the groups ($P>.05$; Table 2).

Female offspring. A significant increase in proceptivity during estrus was detected (characterized by hopping, darting, and ear-wiggling in the presence of the male) in the F1 females offspring of SR parental females compared with CTRL

TABLE 1

Effects of paradoxical sleep deprivation (PSD) or sleep restriction (SR) on sexual behavior of male offspring.

Experiment	Group	Mount latency (s)	Intromission latency (s)	Ejaculation latency (s)	Total no. of mount	Total no. of intromission	Total no. of ejaculation
1	CTRL	151.6 ± 97.4	311.3 ± 141.6	1,535.3 ± 118.4	15.3 ± 2.5	11.5 ± 2.4	0.5 ± 0.2
	SR	275.1 ± 131.8[a]	482.5 ± 181.0	1,438.8 ± 165.2	9.6 ± 2.4[a]	11.3 ± 2.5	0.8 ± 0.4
2	CTRL	181.8 ± 89.0	502.6 ± 163.3	1,344.1 ± 150.0	13.6 ± 2.5	7.6 ± 1.6	0.6 ± 0.2
	SR	560.2 ± 203.4[a]	728.3 ± 210.0	1,532.1 ± 128.0	9.4 ± 2.3[a]	7.1 ± 1.8	0.4 ± 0.2
	PSD	708.4 ± 209.2[a]	1,056.8 ± 209.2[a,b]	1,554.1 ± 119.9	6.1 ± 1.9,	5.0 ± 1.8[a]	0.4 ± 0.2

Note: CTRL = control.
[a] Significant ($P<.008$) difference compared with respective control group in same experiment.
[b] Significant difference compared with SR group ($P<.01$).

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TABLE 2

Effects of paradoxical sleep deprivation (PSD) or sleep restriction (SR) on hormonal concentrations of male offspring.

Experiment	Group	Testosterone (ng/mL)	Progesterone (ng/dL)
1	CTRL	1,216.6 ± 81.3	13.2 ± 1.1
	SR	1,162.6 ± 99.7	10.1 ± 1.0[a]
2	CTRL	424.1 ± 69.3	9.4 ± 0.3
	SR	316.7 ± 58.6	8.7 ± 0.7
	PSD	264.5 ± 34.4[a]	8.5 ± 0.8

Note: CTRL = control.
[a] Significant ($P<.05$) difference compared with control group of the same experiment.

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($P<.0001$; Table 3). Furthermore, these F1 females displayed disrupted sexual behavior, characterized by mounting the males several times throughout the tests. No significant differences were observed in latency to accept the 10 mounts made by the male and receptivity ($P>.05$; Table 3). Testosterone and P evaluation did not differ between the groups ($P>.05$; Table 4).

Experiment 2: Sexual Behavior and Hormones in Offspring from CTRL, PSD, or SR males

Male offspring. F1 males from PSD or SR parental males took significantly longer to initiate the first mount compared with F1 male offspring of CTRL males ($P<.03$ and $P<.0001$, respectively; Table 1). There was also a significant increase in latency to intromission in the F1 male offspring of PSD parental males compared with F1 offspring of CTRL and SR parental males ($P<.003$ and $P<.03$, respectively; Table 1). Also noted was a significant decrease in the total number of mounts in the F1 males from PSD parental males compared with F1 males of CTRL and SR parental males ($P<.0001$ and $P<.05$, respectively; Table 1) and a fall in the total number of intromissions compared with CTRL ($P<.03$; Table 1). No significant difference was observed in latency to ejaculation and total number of ejaculations (Table 1). As for hormones, there was a significant decrease in T in F1 males from PSD parental males compared with CTRL ($P<.05$; Table 2).

Female offspring. F1 females from SR or PSD parental males behaved more receptively than did the CTRL F1 female offspring in the estrus phase ($P<.003$ and $P<.002$, respectively; Table 3). No significant differences were observed in proceptivity and the length of time it took to accept ten mounts by the male ($P>.05$; Table 3), nor in T and P concentrations in all groups ($P>.05$; Table 4).

DISCUSSION

Inadequate sleep is a ubiquitous problem among the population as a whole. Several studies have linked the reduction in sleep to the occurrence of some disturbances affecting both genders (23–26). Considering that the lack of sleep affects women as much as men, the current investigation examined the sexual response of the offspring of female rats who were subjected to SR throughout pregnancy and, separately, of male rats submitted to a PSD or SR protocol before copulation.

Our results demonstrate that the lack of sleep during pregnancy may compromise sexual behavior in the offspring when they reach adulthood. Observations made herein revealed marked differences in the sexual behavior of CTRL and SR groups of F1 offspring. F1 male offspring of female rats that were subjected to SR throughout pregnancy showed significantly reduced sexual motivation, made evident by the increased latency to the first mount and a reduction in the overall number of mounts during the experimental test. Such results may be a consequence of the reduced P concentration that was noted in this group. In contrast, when the parental males were subjected to PSD or SR, the F1 male offspring displayed depressed sexual function accompanied by a reduction in T.

Testosterone has been singled out as the main hormone driving sexual performance in males (performance and attraction) (22, 27–30), but little attention had been devoted to the examination of the role of P, classically associated with the sexual behavior of females, in the

TABLE 3

Effects of paradoxical sleep deprivation (PSD) or sleep restriction (SR) on sexual behavior of female offspring.

Experiment	Group	Cycle	Receptivity (%)	Proceptivity (%)	Latency to complete 10 mounts (s)
1	CTRL	Proestrus	65.0 ± 1.2	69.2 ± 0.1	676.5 ± 87.6
		Estrus	0.0 ± 0.1[a]	0.0 ± 0.0[a]	562.7 ± 103.8
	SR	Proestrus	76.0 ± 1.2	71.4 ± 0.1	570.1 ± 75.0
		Estrus	20.0 ± 1.0[a]	14.2 ± 0.1[a,b]	647.0 ± 59.7
2	CTRL	Proestrus	75.0 ± 2.5	75.0 ± 0.3	203.3 ± 95.2
		Estrus	0.0 ± 0.0[a]	0.0 ± 0.0[a]	714.3 ± 252.6
	SR	Proestrus	60.0 ± 2.7	60.0 ± 0.3	394.4 ± 89.1
		Estrus	27.0 ± 0.0[a,b]	33.3 ± 0.0[a]	391.0 ± 49.9
	PSD	Proestrus	35.0 ± 2.3	25.0 ± 0.3	776.5 ± 121.2
		Estrus	15.0 ± 0.0[a]	16.7 ± 0.0[a]	528.0 ± 132.6

Note: Results were obtained during 2 different estrous cycle phases: proestrus (receptivity phase) and estrus (nonreceptivity phase). CTRL = control.
[a] Significant ($P<.01$) difference compared with proestrus phase.
[b] Significant ($P<.0001$) difference compared with the control group of the same experiment in estrus phase.

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TABLE 4

Effects of paradoxical sleep deprivation (PSD) or sleep restriction (SR) on hormonal concentrations of female offspring.

Experiment	Group	Cycle	Testosterone (ng/mL)	Progesterone (ng/dL)
1	CTRL	Proestrus	103.3 ± 4.0	35.6 ± 2.9
		Estrus	105.7 ± 3.5	35.4 ± 2.6
	SR	Proestrus	117.8 ± 12.0	40.8 ± 0.0
		Estrus	102.1 ± 3.0	37.5 ± 3.2
2	CTRL	Proestrus	57.4 ± 3.3	37.1 ± 2.5
		Estrus	62.4 ± 7.2	24.9 ± 5.6
	SR	Proestrus	61.7 ± 5.4	31.8 ± 5.8
		Estrus	54.1 ± 3.7	30.0 ± 7.4
	PSD	Proestrus	61.3 ± 3.2	32.9 ± 4.1
		Estrus	58.8 ± 5.1	33.4 ± 5.5

Note: Results were obtained during two different estrous cycle phases: proestrus (receptivity phase) and estrus (nonreceptivity phase). CTRL = control.

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sexual behavior of male rats. However, previous studies conducted by our group revealed an unexpected role for this hormone in males (31, 32). We observed that administration of P set off a host of sexual responses in castrated rats even in the absence of other steroids. These results are in line with our observation of reduced P and sexual motivation in the absence of T changes in F1 male offspring of SR females. Therefore, we propose that P may be a relevant factor for male sexual motivation, at least in rats (4, 22, 33).

In addition to influencing copulation behavior in males, we have also reported that P is involved in ejaculation mechanisms in rats deprived of sleep. For example, rats that presented normal ejaculation frequency had higher concentrations of P than did those with low ejaculatory frequency (5, 22), a fact that indicates that an ideal concentration of P is required for satisfactory copulation. It can therefore be said there is evidence that good sexual performance is accompanied by high concentrations of P, and that this may be a limiting factor in sexual motivation in male rats (5, 22). Of note is the observation that there was a reduction in sexual motivation in F1 males from PSD or SR parental males in the absence of any significant concentrations of P. The possible alterations in P may have been masked by the great intragroup variability among these subjects (Tables 1 and 2). Nonetheless, we suggest that the reduction in sexual motivation observed in the offspring may be influenced by the parents. Still, in humans, it is difficult to separate the effects of paternal genetic makeup from those of the father's environmental exposures on offspring, including variations in paternal nutritional, metabolic, and hormonal status (34). It is known that parental environmental exposures can also affect offspring phenotype (35) and that high levels of reactive oxygen species decrease sperm mitochondrial respiration (36). Together, this indicates that fathers can initiate intergenerational transmission of reproduction, induced indirectly or directly, such as through exposure to sleep loss.

Although there was less sexual motivation in F1 males from females subjected to SR throughout pregnancy, there was no compromise in sexual performance in this group compared with the CTRL group. This is most likely because there was not a significant reduction in the concentration of T. However, in the F1 males from SR parental males, we observed a reduction in sexual performance while T concentrations remained unaltered. Several studies reinforce the importance of balance in the concentration of testosterone so that sexual performance is not compromised (5, 22, 27 [review]). Still, other hormones are associated with male sexual performance, such as E_2 (37, 38). Factors such as stress and lack of sleep activate the adrenal-hypothalamus-hypophysis axis, which alters the activity of the aromatase enzyme responsible for the conversion of E_2 to T within the hypothalamus (37). The decreased sexual performace in F1 male offspring of SR males may be due to an imbalance in this enzyme.

There were notable overall differences in the sexual response of F1 females obtained from females and males subjected to either PSD or SR. In the F1 offspring of either PSD or SR parental males there was a significant increase in the acceptance of the male during the nonreceptive phase (the estrus phase), in contrast to what was observed in the CTRL group. Notably, the F1 females from the SR group also displayed disrupted sexual behavior, characterized by several mounts of the males during all tests. Such mounting behavior is, of course, typically a male behavior. We had previously demonstrated that females subjected to PSD also presented increased sexual responses depending on the phase of the estrus cycle. For example, when females were subjected to PSD in the proestrus phase, they displayed heightened receptivity (8). However, no significant differences were observed in the concentrations of T and P in F1 females.

When taken as a whole, the most plausible explanation for our results is that the stress experienced by the parents, due to SR/PSD, gave rise to the alterations in the sexual response observed in all of the offspring groups. It is known that stress is an inherent part of lack of sleep and may lead to compromised functions in the offspring. Several studies have shown that increased corticosterone in the mother during pregnancy may lead to anxiety, obesity, and attention deficits in the offspring, regardless of gender (39–41). Glucocorticoids are essential in the normal development of the brain, and several brain structures, such as the anterior pituitary and the hypothalamus, house receptors sensitive to these substances. Thus, prenatal exposure to stressful factors may influence development. In turn, such altered development might be at the root of the alterations observed in the hypothalamic-pituitary-adrenal axis, which is responsible for behavioral and neuroendocrine function in adulthood, including sexual response.

The present investigation demonstrated that sleep restriction suffered by parents leads to long-lasting consequences in the offspring, jeopardizing the sexual responses of the first generation, including hormonal alterations in both sexes of offspring, reductions in sexual drive in the F1 male, and altered sexual behavior in the F1 female. This study sought to reset the scope of the consequences of sleep shortage and stress, which, as it demonstrates, are far-reaching to the point of affecting descendants. It is

important to be aware of the adverse effects that poor sleep has upon sexual function in the offspring, and to understand that the benefits of quality sleep extend beyond individuals to their descendants.

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