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More than hormones: Sex differences in cardiovascular parameters after sleep loss in rats

Gabriela Matos [a,1], Neuli M. Tenório [a,1], Cássia T. Bergamaschi [b], Ruy R. Campos [b], Fátima Cintra [a], Sergio Tufik [a], Monica L. Andersen [a,*]

[a] Departamento de Psicobiologia — Universidade Federal de São Paulo, Brazil
[b] Departamento de Fisiologia — Universidade Federal de São Paulo, Brazil

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ABSTRACT

Although the influence of sex on sleep pattern and cardiovascular parameters is well known, knowledge regarding the effects of sleep loss on heart responses in both sexes is scarce. The present study investigated the effects of paradoxical sleep deprivation (PSD) and chronic sleep restriction (SR) on cardiovascular parameters and adrenocorticotropic hormone (ACTH) levels in male and female rats. Both groups were randomly assigned to PSD for 96 h, SR for 21 days or home-cage control. Mean arterial pressure (MAP), heart rate (HR), baroreflex sensitivity (bradycardia and tachycardia responses) and ACTH levels were evaluated. The results showed that PSD induced a significant increase in HR and ACTH levels in both sexes, although male rats presented higher levels of ACTH hormone compared to females. In addition to sex-specific responses, PSD decreased the tachycardia only in male rats. SR, induced a significant increase in MAP and decrease in bradycardia in both sexes. Male rats were more affected by sleep deprivation protocols than females for MAP, bradycardia response, and ACTH levels. The results showed that the effects of sleep loss on cardiovascular parameters are associated with the protocol of sleep deprivation and that sex can modulate these effects. We suggested this experimental model as a suitable tool for further investigations of the relationship between cardiovascular parameters and sleep.

1. Introduction

It is established that sex influences the sleep pattern in healthy subjects and patients with sleep disorders (Goel et al., 2005; Silva et al., 2008; Tufik et al., 2010; Zimberg et al., 2011). Furthermore, from 1985 to 2006, the percentage of individuals who reported a significant reduction in sleep (≤6 h) increased between the ages 30–64 years in both sexes (CDC, 2005). Even with the chronic sleep deprivation imposed by lifestyle (Bonnet and Arand, 1995; CDC, 2011; Tufik et al., 2009), little attention has been given to the short and long-term physiological consequences of sleep loss between the sexes. In clinical research, studies have found that healthy woman appear to have better sleep quality than men (Goel et al., 2005; Zhang et al., 2011); however women of all adult ages report more sleep problems, including inadequate sleep time and insomnia (Gras et al., 2009; Santos-Silva et al., 2012; Silva et al., 2008).

Reduction of sleep induces changes in behavioral, neurochemical, and genetic parameters in both animals and humans (Andersen et al., 2010, 2011; Guindalini et al., 2009; Martins et al., 2010; Novati et al., 2012; Pellegrino et al., 2012; Yang et al., 2012). Furthermore, sleep can modulate other physiological parameters, such as cardiovascular function (Tenório et al., in press). Sleep restriction (SR) induced an increase in renal sympathetic nervous system activation associated with a reduction in plasma angiotensin (1–7) concentrations, which in turn could modulate the pathological cardiovascular response (Perry et al., 2011a). Sleep loss also modulates blood parameters for cardiovascular risk, such as blood viscosity and cholesterol fractions (Andersen et al., 2004; Everson and Szabo, 2011). These parameters may be regulated by different mechanisms in both sexes, since the level of circulating lipoproteins after sleep loss show sex-differences (Antunes et al., 2007).

Differences between sexes are not restricted to sleep research. In cardiovascular studies, it has been described that the incidence of cardiovascular disease is higher in men than women (Vitale et al., 2009). Differences in hormones, tissue, and cells were attributed as a protective factor in female group (Vitale et al., 2009). Indeed, baroreflex sensitivity (the mechanism by which autonomic nervous system detects and regulates acute blood pressure changes) is influenced by female hormones, since older women presented changes in cardiovascular parameters when compared to a young group (Barnes et al., 2012). Reduction

Abbreviations: ACTH, adrenocorticotropic hormone; CTRL, control group; HR, heart rate; MAP, mean arterial pressure; PSD, paradoxical sleep deprivation; SR, sleep restriction.

* Corresponding author at: Rua Napoleão de Barros, 925, Vila Clementino, SP 04024-002, São Paulo, Brazil. Tel.: +55 11 2149 0155; fax: +55 11 5572 5092.
E-mail addresses: ml.andersen12@gmail.com, mandersen@unifesp.br (M.L. Andersen).

[1] Authors contributed equally to this manuscript.

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in baroreflex sensitivity has been associated with impaired regulation of blood pressure, hypertension, and increased risk of cardiovascular disease-related mortality (Dangardt et al., 2011; Martinez et al., 2011; Shamsuzzaman et al., 2003; Timmers et al., 2003).

According to the aforementioned, the sex matters in the sleep pattern and well as in the consequence of sleep deprivation. However, investigations regarding this issue are scarce. In view of the fact that there were sex differences in sleep pattern, as well as in cardiac function, we hypothesized that the heart response would be impaired in sleep deprived males rats, since there is evidence of the protective effect of female hormones. Thus, the purpose of this study was to investigate the consequences of acute and chronic sleep deprivation on cardiovascular parameters and ACTH levels in male and female rats.

2. Materials and methods

2.1. Animals

Experiments were performed in male and female Wistar rats, aged 3 months, provided by the Centro de Desenvolvimento de Modelos Experimentais para Medicina e Biologia (CEDEME) at Universidade Federal de São Paulo. Throughout the study, the experimental room was kept at controlled temperature (22 ± 1 °C) and a 12:12 h light–dark cycle (lights on at 07:00 h). Food and water were provided ad libitum. All procedures in the present study complied with recommendations in *Animal Models as Tools in Ethical Biomedical Research* (Andersen and Tufik, 2010). The study was approved by the Ethical Committee of Universidade Federal de São Paulo (CEP 1268/08).

2.2. Vaginal cytology

Differences in vaginal epithelial cell morphology (leukocytes, cornified cells and nucleated epithelial cells) from vaginal smears were used to differentiate the phases of estrous cycle. The first phase, proestrus, was characterized by many nucleated epithelial cells and few leukocytes, followed by estrus with many cornified cells without leukocytes. The last phase, diestrus, was identified by the presence of few nucleated epithelial cells and many leukocytes. Vaginal smears were conducted during the 15 days (once a day) before the experiment, in order to control the baseline estrous cycle of each female. The rats that had 2 regular cycles were selected. All samples were taken between 08:00 and 9:00 h. All rats started the experiments in the diestrus phase of the estrous cycle. This phase has been previously reported to be particularly affected by paradoxical sleep deprivation (PSD) with a disruption of the cyclicity of the estrous cycle after a PSD protocol (Antunes et al., 2006).

2.3. Paradoxical sleep deprivation

Society is constantly exposed to sleep loss due to professional demands and social events which, in turn, results in acute sleep deprivation. For this purpose, we performed the PSD by modified multiple platform method, in order to model a single event of sleep deprivation. Male and female groups were submitted to PSD over a period of 96 h by being placed on circular platforms (6 cm in diameter) 1 cm above water level in a cage (23 × 23 × 29 cm). Muscle atonia caused them to fall off the platform and awaken whenever paradoxical sleep occurred. This sleep protocol is effective in producing total suppression of paradoxical sleep (Machado et al., 2004). Throughout the study, the experimental room was kept at controlled temperature (22 ± 1 °C) and a 12:12 h light–dark cycle (lights on at 07:00 h). Food and water were provided ad libitum and the water in the tank was changed daily. The control (CTRL-1) groups were housed in similar cages containing bedding in the same room as the experimental rats.

2.4. Sleep restriction

Some individuals suffer from chronic sleep deprivation induced by pathologies and sleep disturbances. Of note, a high prevalence (32.8%) of obstructive sleep apnea syndrome was observed in an extensive epidemiological study (Tufik et al., 2010). The SR protocol models this common situation in the modern society. SR protocol consisted of submitting the rats to chronic and partial sleep deprivation for 18 h (beginning at 16:00 h and terminating at 10:00 h of the next day) for 21 days (Machado et al., 2006). The protocol of SR is very similar to the PSD protocol described above, except for the duration (96 consecutive hours for PSD; 18 h daily for 21 days for SR). After every 18 h of SR, rats were allowed to sleep for 6 h (sleep window). A separate control group (CTRL-2) was used to evaluate the effect of SR on cardiovascular responses.

2.5. Experimental design

Male and female rats were randomly assigned to PSD, SR (n = 7–12/group) or control (CTRL; kept their in home cages) groups (n = 9–12/group). After the PSD, SR, or equivalent period in CTRL groups, male and female animals underwent surgical procedures. The rats were initially anesthetized by halothane inhalation (5%) and were maintained in a mix of 3% halothane with 100% O_2. Tapered polyethylene catheters (PE-50) were placed in the right femoral artery to monitor arterial pressure and in the right femoral veins to infuse drugs. When the animals returned to their normal physiological functions, baseline values of mean arterial pressure and heart rate were recorded for 5 min in conscious and freely moving rats. Then, each animal received 3 bolus injections intravenous (0.1 ml) of phenylephrine (30, 50 and 100 μg/ml) and 3 bolus of sodium nitroprusside (50, 150 and 200 μg/ml) in random order and minimum interval between the doses was of 5 min.

The changes between baseline and peak values of the mean arterial pressure (MAP) and the changes in heart rate (HR) reflex in response to pressor (phenylephrine) and depressor (sodium nitroprusside) injections were used to quantify baroreflex sensitivity (beat/mm Hg) through the ΔHR/ΔMAP relationship for each animal.

2.6. Blood sampling and hormone analysis

Another set of animals was used in order to determine the ACTH levels. PSD, SR, and CTRL conditions were carried out as described above. Immediately after the PSD (n = 9–10/group), SR (n = 7–12/group) or equivalent period in CTRL group (n = 9/group) (CTRL-3), the animals were brought to an adjacent room and decapitated between 09:00 and 11:00 h. Some rats from CTRL group were decapitated each day along with those of PSD and SR groups. Blood was collected in sterile glass tubes with EDTA and centrifuged to obtain samples of plasma. The samples were maintained at −20 °C until the assays. ACTH concentrations were determined by a sequential chemiluminescent immunometric method using a monoclonal murine antibody specific for ACTH (DPC Immulite, Los Angeles, CA, USA). The sensitivity of the assay is 5 pg ml^{-1}.

2.7. Statistical analysis

All the variables were tested first for normality and homogeneity. Those that did not fit the normal and homogenous distribution ($p<0.05$ in Kolmogorov–Smirnov and Levene's tests, respectively) were converted into Z-scores. For cardiovascular parameters and blood sampling, 2-way analysis of variance (ANOVA) tests were conducted to determine differences between sleep deprivation protocols (PSD, SR and CTRL) and sex (male and females) followed by Bonferroni *post hoc* tests when necessary. The level of significance was set at 5%. Data are reported as mean ± standard deviation.

3. Results

3.1. Cardiovascular analysis

In order to facilitate the comprehension, the cardiovascular parameters (MAP, HR and baroreflex sensitivity) were described separately.

3.1.1. Mean arterial pressure

Sleep loss induced significant alterations in MAP in both male and female rats [$F(2,50) = 6.39$; $p<0.01$]. Sleep restriction procedures significantly increased MAP when compared to respective CTRL in both sexes ($p<0.02$) (Fig. 1). Acute PSD did not result in significant alteration in MAP. Even with the marked alterations in SR, there was no significant difference between sexes due to experimental procedures [$F(2,50) = 0.03$; $p>0.05$]. When compared between sleep deprivation protocols, MAP was significantly higher in SR than PSD in the male rats ($p<0.05$) (Fig. 1). On the other hand, the difference between PSD and SR protocols was not detected in the female group ($p>0.05$).

3.1.2. Heart rate

Sleep-deprived rats showed significant differences in HR [$F(2,50) = 15.34$; $p<0.001$]. Pos-hoc test revealed that there was a significant increase in HR in male and female rats submitted to PSD when compared to respective CTRL ($p<0.01$) (Fig. 2). Chronic SR did not induce significant changes in HR in male and female rats ($p>0.05$). Furthermore, HR was similar between sexes [$F(2,50) = 0.359$; $p>0.05$].

3.1.3. Baroreflex sensitivity: bradycardia response

The baroreflex function was significantly affected by experimental procedures [$F(2,50) = 9.34$; $p<0.01$]. Male and female rats submitted to SR showed a significant reduction of bradycardia response when compared to respective CTRL ($p<0.01$). In contrast, PSD did not modulate this parameter in either sex. Male and females rats showed similar pressure response to sodium nitroprusside injection [$F(2,50) = 0.50$; $p>0.05$]. SR induced a statistical effect compared to PSD only in male rats ($p<0.005$) (Fig. 3).

3.1.4. Baroreflex sensitivity: tachycardia response

Sleep deprivation protocols resulted in significant baroreflex changes in rodents [$F(2,50) = 15.45$; $p<0.001$]. Pos hoc test revealed that only PSD induced a significant reduction of tachycardia response in male rats ($p<0.01$) (Fig. 4). Neither PSD and SR induced changes in this parameter in the female groups ($p>0.05$). Tachycardia did not differ significantly between the sexes [$F(2,50) = 3.46$; $p>0.05$].

3.2. ACTH levels

The levels of ACTH in the plasma was significantly higher in males when compared to females [$F(1,50) = 19.40$; $p<0.001$] (Fig. 5). In addition, this hormone was modulated by sleep loss in both groups [$(F = 2,50) = 17.23$; $p<0.001$]. Post-hoc tests revealed that there was a significant increase in ACTH in both sexes submitted to PSD when compared to respective CTRL ($p<0.004$) (Fig. 5). The effect of PSD was significantly higher than SR in male rats ($p<0.001$). SR did not significantly affect the ACTH levels in any group when compared to home-cage controls.

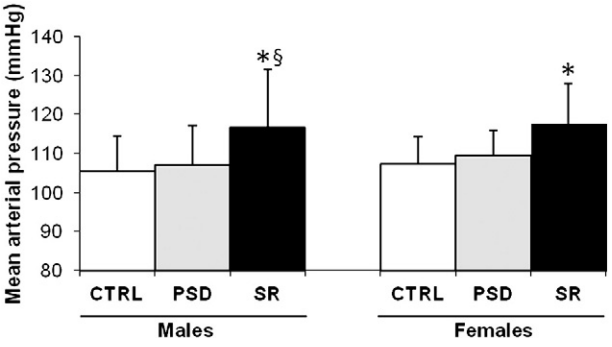

Fig. 1. Mean ± SD values of mean arterial pressure [mm Hg] in control (CTRL), paradoxical sleep deprived (PSD), and sleep restricted (SR) male and female rats. *$p<0.05$ when compared to respective CTRL group. §$p<0.05$ when compared to PSD group.

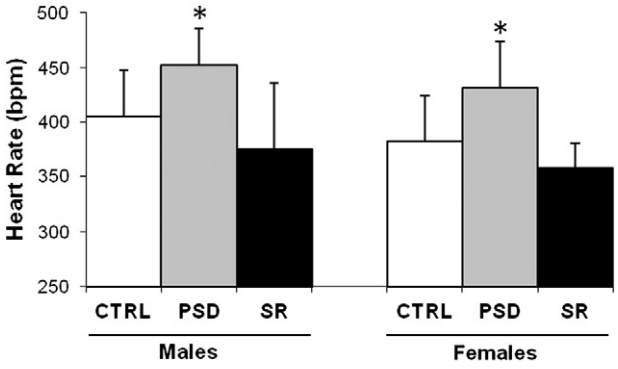

Fig. 2. Mean ± SD values of heart rate [bpm] in control (CTRL), paradoxical sleep deprived (PSD), and sleep restricted (SR) male and female rats. *$p<0.05$ when compared to respective CTRL group.

4. Discussion

Sleep deprivation protocols induced significant changes according to duration of protocol and sex. PSD induced increases in HR and ACTH in both male and female groups, whereas the reduction of tachycardia response was significant only in male rats. At the same time, the SR protocol resulted in an elevation of MAP and attenuation of the bradycardia response in all groups. Interestingly, the effects of sleep loss was more evident in the male group, which presented statistical differences between the PSD and SR conditions in MAP, bradycardia response, and ACTH levels. For sex differences, the level of ACTH was higher in male than female rats.

Regarding acute selective PSD, both sexes showed an increase in ACTH levels and HR. Our data reproduced the results published by Machado et al. (2008) in male rats. Additionally, the present study revealed that female rats presented similar responses for ACTH levels and HR after sleep loss. We suggested that the increase in ACTH is probably due to activation of the hypothalamic–pituitary–adrenal axis by the sleep loss. This augmentation stimulates the autonomic nervous system, which, in turn, releases catecholamines and consequently increased the HR. The hypothesis is supported by the increase in circulating levels of norepinephrine and epinephrine during partial sleep deprivation in healthy male individuals (Irwin et al., 1999) and rodents (Andersen et al., 2005). Additionally, it has been suggested that sympathetic system activation (induced by sleep loss) can modulate the development of hypertension (Perry et al., 2011a,b).

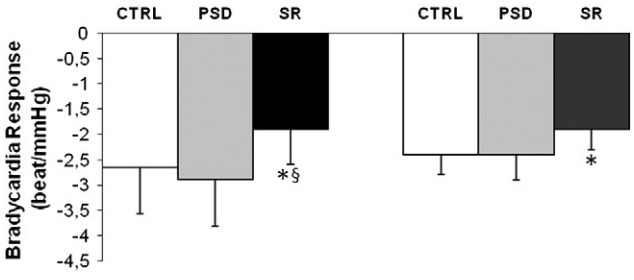

Fig. 3. Mean ± SD values of vagal gain [beat/mm Hg] in control (CTRL), paradoxical sleep deprived (PSD), and sleep restricted (SR) male and female rats. *$p<0.05$ when compared to respective CTRL group. §$p<0.05$ when compared to PSD group.

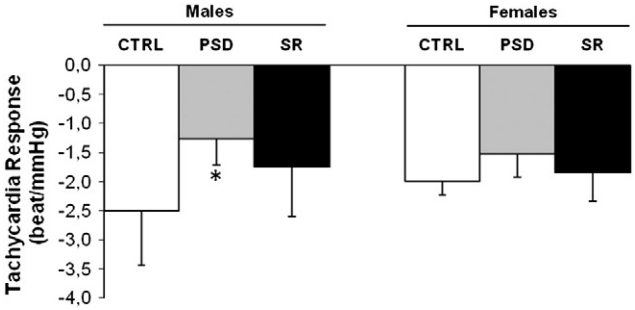

Fig. 4. Mean ± SD values of sympathetic gain [beat/mm Hg] in control (CTRL), paradoxical sleep deprived (PSD), and sleep restricted (SR) male and female rats. *p<0.05 when compared to respective CTRL group.

Recently, it was showed that women had significantly reduced cardiovascular risk (myocardial infarction and cardiovascular death) when compared to men in an extensive follow-up study with more than 30,000 subjects (Kappert et al., 2012). Along the same lines, 67% of patients with previous cardiovascular afflictions who died suddenly after myocardial infarction were men (Solomon et al., 2005). Even with the great knowledge concerning cardiovascular differences between men and women, the reasons for changes in cardiovascular parameters according to sex is largely unknown and opens a new avenue for research (Dunlay and Roger, 2012). In this sense, our data showed a general increase in the ACTH levels of male compared to female rats. This fact could explain the significant sex-difference observed between sleep deprivation protocols in MAP and bradycardia response.

The present study revealed the impairment of the tachycardia response in males after PSD. In view of that fact that the baroreflex sensitivity is an important marker for cardiovascular diseases (Bruno et al., 2012; La Rovere et al., 1998; Rubinger et al., 2012), and female rats were less affected, it can be accepted that female sex hormones can protect the cardiovascular system. The hypothesis is supported by preclinical and clinical studies in the current literature. Sex differences was found in baroreflex sensitivity and blood cardiovascular risk in rodents and humans (Antunes et al., 2006; Barnes et al., 2012; Bjerregaard, 2013; El-Mas et al., 2011,2012). Collectively, the modulator role of female hormones against cardiovascular affections as well as their influence on sleep pattern have been reported (Andersen et al., 2011; Antunes et al., 2006; Booth and Lucchesi, 2008; Gökkuşu et al., 2012; Kallen and Pal, 2011).

Chronic sleep loss induced the augment of MAP and reduction in bradycardia response in male and female rats. It is important to highlight that SR mimics the chronic sleep deprivation induced by modern society behavior and/or sleep disturbance (CDC, 2005; Tufik et al., 2009; 2010; Young et al., 2009). Clinical studies provide many examples of SR effects. For instance, long-term SR induced the production of pro-inflammatory cytokines, and increased HR and C-reactive protein, which may increase the risk of developing cardiovascular diseases (van Leeuwen et al., 2009). Animal models for SR suggest that increased sympathetic nervous system activation and reduction of plasma angiotensin (1–7) concentrations may impaired the cardiovascular functions (Ferrario, 2006; Perry et al., 2011a,b).

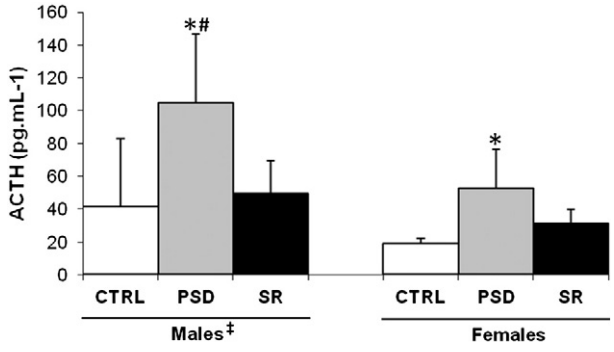

Fig. 5. Mean ± SD concentration of adrenocorticotropin (ACTH) [pg ml^{-1}] in control (CTRL), paradoxical sleep deprived (PSD), and sleep restricted (SR) male and female rats. ‡p<0.05 when compared between genders. *p<0.05 when compared to respective CTRL group. #p<0.05 when compared to SR group.

Taken together with previous reports, the present study showed that the effects of sleep loss on cardiovascular parameters are associated with the protocol design of sleep deprivation (PSD or SR) and that sex can modulate the effects. In view of the high applicability of this data when compared to clinical findings, we suggested our experimental model as a suitable tool for investigations of the relationship between cardiovascular parameters and sleep.

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