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Differential sympathetic activation induced by intermittent hypoxia and sleep loss in rats: Action of angiotensin (1–7)

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ABSTRACT

The present study attempted to evaluate the effects of chronic intermittent hypoxia (CIH) associated with sleep restriction in hemodynamic parameters and the plasma renin–angiotensin system. Wistar–Hannover rats were submitted to isolated CIH exposure (1000–1600 h), sleep restriction (1600–1000 h), defined as 18-h paradoxical sleep deprivation followed by 6-h sleep permission period and CIH associated to sleep restriction for 21 days. The CIH and sleep restriction group showed a preferential increase in renal sympathetic nervous system (rSNA) associated with a reduction in plasma angiotensin (1–7) concentrations. However, CIH-sleep restriction rats did not modify rSNA and showed a higher angiotensin (1–7) concentration when compared to isolated CIH and sleep restriction. These results suggest that CIH and sleep restriction impaired the cardiovascular system, and its association to sleep loss can modify these effects by partially restoring circulating angiotensin (1–7).

1. Introduction

Obstructive sleep apnea has been recognised as an independent risk factor for hypertension (Lavie et al., 2000). However, the mechanism by which sleep apnea can lead to hypertension and other cardiovascular risk factors is not clear. Animal experimental data suggests that chronic intermittent hypoxia (CIH) provides the causal link between upper airway obstruction during sleep and sympathetic activation during waking hours (for review see Weiss et al., 2007). It appears that both the adrenal gland, via circulating epinephrine, and the renin–angiotensin system (RAS) participate in diurnal arterial hypertension in subjects with apnea (Fletcher et al., 2002).

RAS is a regulator of cardiovascular and renal systems and its components are implicated in the control of blood pressure, body fluid homeostasis and several other cardiovascular functions (Inagami, 1994). Angiotensin-converting enzyme-2 (ACE2) efficiently hydrolyzes angiotensin II (Ang II) into angiotensin 1–7 [Ang (1–7)] (Zisman et al., 2003; Rice et al., 2004; Santos and Ferreira, 2007), but it is unclear how Ang (1–7) may contribute to the regulation of cardiovascular function both physiologically and pathologically (Ferrario, 2006). Ang (1–7), a bioactive peptide in the renin–angiotensin system, has regulatory actions counter to Ang II. Ang (1–7) is capable of both activation of peripheral vasodilator mechanisms and antitrophic effects mediated by inhibition of protein synthesis (Ferrario et al., 2005; Santos and Ferreira, 2007). The mechanisms underlying the Ang (1–7) induced vasorelaxation are the potentiation of bradykinin-induced dilation, the stimulation of vasodilator prostaglandins and the mediation of NO-release (for review Schindler et al., 2007). However, in this emerging field of Ang (1–7) research, limited information about the functions of this bioactive peptide currently exists, particularly in cardiovascular responses to sleep apnea.

Isolated effects of hypoxia in animal models have been the subject of extensive research. However, sleep apnea is characterised by a collapse of upper airway breathing associated to sleep fragmentation. Recently, our group developed a rodent model that evaluated the effects of CIH associated with sleep restriction and provided important new insights in this field (Perry et al., 2007, 2008). Thus, we attempt to determine the effects of CIH associated with sleep restriction on heart rate, blood pressure, sympathetic nerve activity and its consequences in the plasma renin–angiotensin system (RAS) in rats.

2. Materials and methods

2.1. Animals

Experiments were performed on 73 male adult Wistar–Hannover rats provided by the Centro de Desenvolvimento de Modelos

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Experimentais para Medicina e Biologia (CEDEME)—Universidade Federal de São Paulo. The animals were housed in groups of five in standard polypropylene cages in a room maintained at 22 °C with a 12:12-h light–dark cycle (lights on at 07:00 h) and allowed free access to food and water. All animal procedures were approved by the University Ethics Committee (CEP no. 0490/04).

2.2. Chronic intermittent hypoxia

Chronic intermittent hypoxia (CIH) was induced in a custom-built chamber (30×20×20 in., Oxycycler model A44X0, Biospherix, Redfield, NY, USA) connected to a supply of O_2 and N_2 gas. Sensors measured O_2 concentration, CO_2 concentration (<0.01%), humidity (40–50%) and temperature (22–24 °C). Inflow of O_2 and N_2 into the chamber was controlled by a computer programmed to produce cycles of 2 min of room air and 2 min of 10% O_2. Rats were subjected to this schedule during the light period (1000–1600 h). The hypoxia procedure used in the present study reduced oxygen saturation to about 50% (Perry et al., 2007).

2.3. Sleep restriction

Rats were individually placed on a circular platform (6.5 cm in diameter) in a cage (23×23×29 cm) filled with water to 1 cm below the platform level. During paradoxical sleep the rats tend to fall off the platform and awaken due to muscular atonia. In this protocol, the rats were kept on the platforms for 18 h (beginning at 1600 h) and allowed to sleep for 6 h (1000 to 1600 h) every day for 21 days. This particular time interval (1000 h to 1600 h) was chosen because it is when paradoxical sleep is at its highest. Thus, there is a partial compensation for the sleep loss (Machado et al., 2005). All animals were exposed to a habituation period on the platforms for 1 h a day for 3 days prior to the commencement of the sleep restriction protocol.

2.4. Experimental design

Rats were randomly assigned to 4 experimental groups: 1) control; 2) CIH; 3) sleep restriction and 4) CIH associated to sleep restriction. Rats (CIH or CIH-sleep restricted groups) were exposure to CIH between 1000 h and 1600 h. The CIH-sleep restricted rats were submitted daily to sleep deprivation for 18 h (from 1600 h to 1000 h) and during the remaining 6 h of the day (from 1000 h to 1600 h), the rats were allowed to sleep in the hypoxia chamber. On day 21 of the experimental period (between 0800 h and 1000 h), rats of each group were submitted to surgical procedures (n=9 per group) or were euthanised by decapitation for blood collection (n=10 per group). The plasma was separated by centrifugation for 10 min at 2000×*g*.

2.5. Surgical procedures

Rats were anesthetized with halothane (2% in 100% oxygen-enriched air) and instrumented with femoral venous and arterial catheters for drug injection and arterial pressure recording, respectively. Catheters were externalized through the neck. The rats were exposure to anesthesia during 20 min to catheterization. One hour later, blood pressure and heart rate were recorded in awake, freely-moving rats. Moreover, recordings were obtained from rats for 20 min to evaluate the basal blood pressure before urethane anaesthesia. The control group was evaluated with the same anaesthesia procedure. A waiting period of 1 h after the catheterization surgery before recording cardiovascular parameters was shown to provide sufficient time for recovery from the depressant effects of anesthesia. This procedure was only elected in an attempt to promote animal well-being, considering that during the sleep deprivation technique the animals were placed on a circular platform that limited their movements. Furthermore, an additional methodological limitation was involved in keeping the rats awake following the recovery from anaesthesia. During this period sleep deprivation was carried out by gentle handling, which involved tapping the cages whenever the animals appeared drowsy.

Mean arterial pressure (MAP) and heart rate signals on freely-moving rats were derived from pulsatile arterial pressure. All signals were recorded on a computer-based data acquisition system (PowerLab system, AD Instruments, NSW, Australia).

2.5.1. Sympathetic nerve activity (SNA)

After recording blood pressure and heart rate in freely-moving rats the animals were anesthetised with urethane (1.2–1.4 g/kg, i.v.). All animals were artificially ventilated with oxygen-enriched air using a respiratory pump, at a concentration that maintained end-tidal CO_2 close to 4%. Rectal temperature was maintained at 37±0.5 °C by means of a servo-controlled electric blanket. The left renal (rSNA) and splanchnic (sSNA) sympathetic nerves were exposed through a left retroperitoneal flank incision, placed on bipolar recording silver electrodes and covered with mineral oil. Signals from the nerves were displayed on an oscilloscope and monitored by means of an audio amplifier. Nerve activity was also amplified (Neurolog, 20 K, UK) using a band-pass filter (50–1000 Hz), rectified and integrated and it is expressed as μV (Representative traces—Fig. 1; Panel C). On completion of the experiments, the baseline noise level of sympathetic nerve activity was determined after administration of hexamethonium bromide (30 mg/kg, i.v.). This procedure allowed discrimination of the background noise from burst activity. The ganglionic blockade technique is the "gold standard" procedure used to determine the background noise level, and thus the zero baseline of an SNA recording (Guild et al., 2009). Nerve discharge during the experiment was expressed as spikes/second. Guild et al. (2009) showed that the burst frequency provides important information and an alternative for comparing the SNA signal among subjects with different baseline microvolt levels. The mean value of spikes frequency was obtained after removing background noise as reported previously by Yang and Coote, 2006. Only experiments in which the level of background noise was confirmed at the end of the experiments following hexamethonium and terminal anesthesia are included in this report (Yang and Coote, 2006).

2.6. Blood collection

2.6.1. Angiotensin quantification by high-performance liquid chromatography (HPLC)

Ang I, II and 1–7 were measured using reverse-phase HPLC (Ronchi et al., 2007) and expressed as nmol/mL.

2.6.2. Angiotensin-converting enzyme activity (ACE)

ACE was determined fluorimetrically using 1 mmol/L Z-Phe-His-Leu as a substrate (Bachem Ltd, Switzerland). The standard assay contained 100 mmol/L potassium buffer, pH 8.3, 100 mmol/L NaCl and 100 μmol/L $ZnSO_4$ and was performed at 37 °C (Friedland and Silverstein, 1976; Casarini et al., 1997).

2.7. Statistical analysis

Values shown are expressed in mean±standard error of mean (SEM). Student-*t* test was used to analyse the data. $P<0.05$ was considered statistically significant.

3. Results

The rSNA activity was higher in CIH ($p<0.04$) and sleep restriction ($p<0.04$) than in the control group, as shown in Fig. 1A. There was no significant difference between CIH-sleep restriction and control

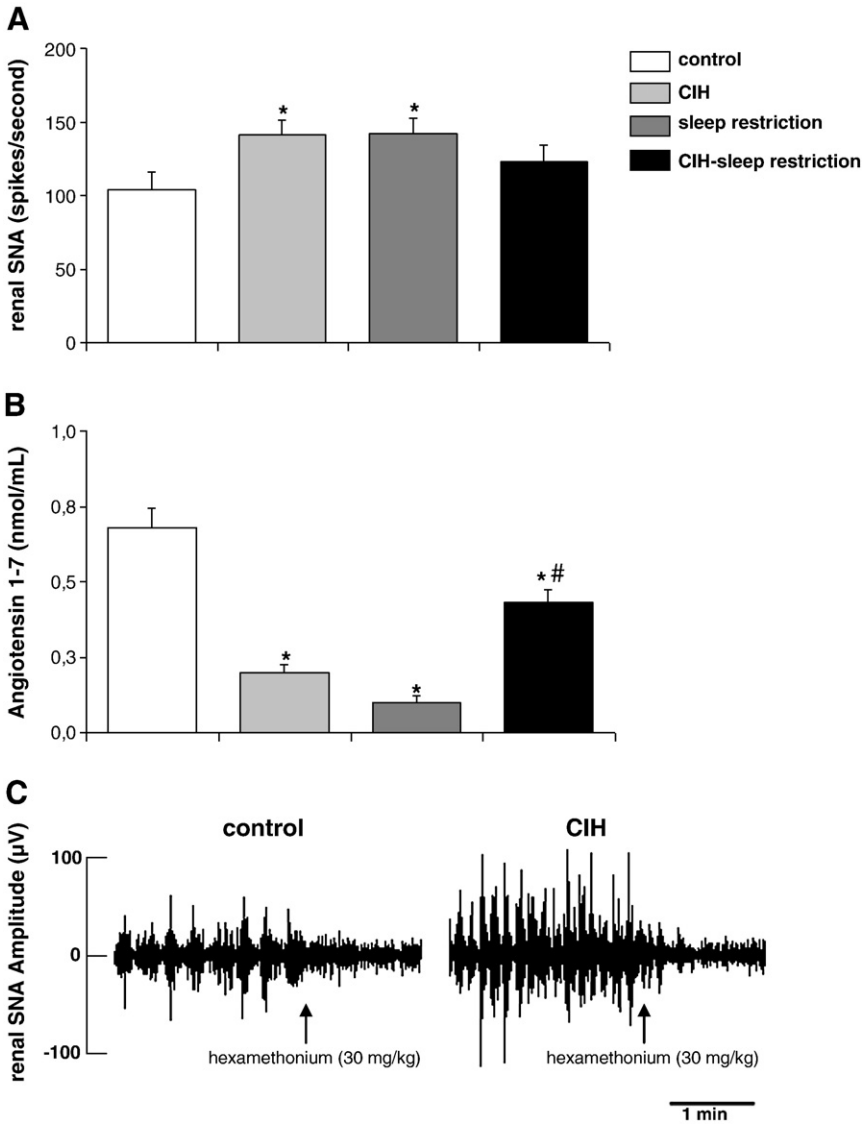

Fig. 1. Effects of chronic intermittent hypoxia (CIH) and chronic intermittent hypoxia associated to sleep restriction (CIH-sleep restriction) on renal sympathetic nerve activity (rSNA —Panel A) and plasma Ang (1–7) concentrations (Panel B). Representative traces of renal sympathetic nerve activity amplitude were expressed as μV (Panel C). Baseline noise level of sympathetic nerve activity was determined after administration of hexamethonium bromide (30 mg/kg, i.v.). *$p<0.05$ compared to the control group and #$p<0.05$ compared to the CIH and sleep restriction groups (Student-*t* test). Data are expressed as mean ± SEM.

groups. Differences among the groups in mean arterial pressure, heart rate and sSNA were not significant (Table 1).

Ang (1–7) values were significantly lower in the CIH ($p<0.001$), sleep restriction group ($p<0.001$) and CIH-sleep restricted ($p<0.01$) groups when compared to the control group, whereas concentrations in the CIH-sleep restricted group were higher than in the CIH and sleep restriction groups ($p<0.001$), as shown in Fig. 1B. No statistically significant difference was observed in plasma angiotensin I, angiotensin II and ACE activity among all groups. Table 1 shows all cardiovascular and hormonal parameters evaluated in the present study.

4. Discussion

The principal findings of our study are that CIH and sleep restriction specifically increased rSNA activity and induced a

Table 1
Effects of chronic intermittent hypoxia (CIH) and chronic intermittent hypoxia associated to sleep restriction (CIH-sleep restriction) on mean arterial pressure (MAP), heart rate (HR), splanchnic sympathetic nerve activity (sSNA) and the plasma renin–angiotensin system.

	Control	CIH	Sleep restriction	CIH-sleep restriction
MAP (mm Hg)	110.5 (±3.6)	107.6 (±3.8)	104.6 (±3.6)	109.0 (±4.3)
HR (bpm)	394.2 (±17.3)	393.7 (±31.2)	385.0 (±22.2)	421.5 (±30.4)
sSNA (spikes/s)	106.4 (±12.6)	110.5 (±20.3)	106.6 (±8.1)	88.8 (±6.5)
Ang I (nmol/mL)	0.8 (±0.1)	0.7 (±0.06)	0.7 (±0.1)	0.6 (±0.07)
Ang II (nmol/mL)	36.4 (±2.6)	36.3 (±2.1)	29.0 (±1.76)	34.3 (±1.7)
ECA (nmol/mL/min)	78.9 (±5.4)	64.4 (±5.9)	76.9 (±7.9)	75.7 (±4.6)

Data are expressed as mean ± EPM. (Student-*t* test was used to analyze the data; N = 7–10/group).

reduction in plasma Ang (1–7) concentrations. However, the CIH-sleep restriction did not modify rSNA activity. Whether or not CIH was associated with sleep loss, reduced plasma Ang (1–7) concentrations were measured compared to control rats. However, values in the CIH-sleep restricted groups were higher than in the CIH and sleep restriction groups.

Studies using animal models have revealed that CIH has an important role in the stimulation of chemoreceptors (Fletcher, 2001; Braga et al., 2006; Weiss et al., 2007; Prabhakar et al., 2007; Dematteis et al., 2008), increasing sympathetic activity and inducing hypertension (Bao et al., 1997; Weiss et al., 2007). With regard to sympathetic activity, CIH rats showed an increase in rSNA whereas no significant alteration in sSNA was observed. CIH-sleep restriction did not modify rSNA or sSNA. Interestingly, isolated sleep restriction induced a selective increase of rSNA activity that was accompanied by a reduction in Ang 1–7. Thus, the data show that the paradigm of isolated CIH and sleep restriction induced alterations in sympathetic nerve activity, preferentially in the kidney.

After 21 days, CIH did not induce alterations in blood pressure. Some authors suggest that the alteration of blood pressure induced by hypoxia possesses a time-dependent effect (Prabhakar et al., 2001, 2005; Hui et al., 2003; Zoccal et al., 2007; Dematteis et al., 2008). For instance, Hui et al. (2003), using a similar hypoxia protocol (room air to 10% of O_2) observed an increase in the blood pressure of rats after a 30-day-intermittent hypoxia period. Moreover, the alterations in markers of the catecholamine biosynthetic pathway in peripheral tissues that directly participate in blood pressure were initiated after a 14-day-intermittent hypoxia period. In fact, different hypoxia protocols (room air to 2% to 5% O_2 for 35 days) showed elevated blood pressure occurring after long-term exposure to intermittent hypoxia (Prabhakar et al., 2001, 2005; Zoccal et al., 2007).

To elucidate the basis for these cardiovascular alterations we evaluated the effects of CIH, sleep restriction and CIH-sleep restriction on the renin–angiotensin system. Our results show that hypoxia did not modify plasma angiotensin I or angiotensin II concentrations. However, Zoccal et al. (2007) verified that ganglionic blockade, combined with antagonism of angiotensin II type 1 receptor (AT1), produced a decrease in blood pressure in CIH rats. Most likely, the time of hypoxia (21 days vs. 35 days) and differences in the severity of hypoxia (5% vs. 10% O_2) have an important role in the cardiovascular response (Li et al., 2007; Perry et al., 2007).

In our study, CIH and sleep restriction markedly reduced plasma Ang (1–7) concentrations and induced a selective increase in rSNA activity. We hypothesise that the decrease in Ang (1–7) concentration after CIH leads to a reduction of its protective effect on the cardiovascular system. These results suggest that a reduction of Ang (1–7), a potent vasodilator counters the effects of Ang II, plays a relevant physiologic role in rSNA and precedes the hypertension in the CIH group. One hypothesis is that the increase in rSNA may be triggered by decreased endogenous Ang 1–7 that has been considered to be a sympathoinhibitory hormone acting in the central nervous system (Silva et al., 1993). Although this interpretation should be considered, the complete comprehension of the interactions between Ang (1–7) and the mechanism that regulates the SNA depends on several other components. Interestingly, Ang (1–7) concentrations were higher in the CIH-sleep restricted group compared to CIH. Moreover, sleep restriction induced an increase in rSNA and a decrease in plasma Ang (1–7) concentrations. However, there was no significant difference in rSNA in the CIH-sleep restricted group. Some studies suggest that Ang (1–7) may act as an endogenous inhibitor of angiotensin II (van der Wouden et al., 2006). Thus, these data suggest that an increase in Ang (1–7) concentrations induced a protective effect on the rSNA, thus implying a direct involvement of Ang (1–7) in cardiovascular control. Probably the ACE2 responsible for the liberation of Ang (1–7) can be upregulated. We cannot exclude that other enzymes able to produce Ang (1–7) can be also upregulated. Clearly, further studies are needed to elucidate other mechanisms that modulated SNA.

One hypothesis to explain our data may be attributed to adaptive responses to hypoxia. Hypoxia is characterised by inadequate oxygen delivery to tissues resulting in an imbalance between the oxygen demand and energy supply. Reduction of O_2 demand, essential for breathing and ATP production, leads to the reduction of cellular activity. Defence mechanisms include erythropoiesis and angiogenesis to augment red blood cell mass and oxygen delivery, and metabolic remodelling that increases utilisation of oxygen-efficient fuel substrates such as carbohydrates (Hochachka, 1998; Ostadal et al., 1999). These mechanisms compensated the deleterious effects of intermittent hypoxia. Corroborating the hypothesis noted by Lavie and Lavie (2006), the age-related decline in mortality in sleep apnea patients can be explained by the activation of a protective adaptive mechanism that is inherent to the nature of the syndrome, namely, preconditioning. Our data suggest that the decrease in cellular metabolism induced by both sleep and low O_2 concentration may be the reason why hypoxia during the consolidated sleep period did not have deleterious effects on the cardiovascular system. Thus, studies specifically utilising a stimulus of hypoxia during sleep are necessary to determine whether the association of hypoxia and disruption of sleep can independently impact the cardiovascular system.

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