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**Provocative motion causes fall in brain temperature
and affects sleep in rats.**

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ABSTRACT

Neural substrate of nausea is poorly understood, contrasting the wealth of knowledge about the emetic reflex. One of the reasons for this knowledge deficit is limited number and face validity of animal models of nausea. Our aim was to search for new physiological correlates of nausea in rats. Specifically, we addressed the question whether provocative motion (40-min rotation at 0.5 Hz) affects sleep architecture, brain temperature, heart rate and arterial pressure.

Six adult male Sprague Dawley rats were instrumented for recordings of EEG, nuchal EMG, hypothalamic temperature and arterial pressure. Provocative motion had the following effects: i) total abolition of REM sleep during rotation and its substantial reduction during the first hour post-rotation (from 20 ± 3 to 5 ± 1.5 %); ii) reduction of NREM sleep, both during rotation (from 57 ± 6 to 19 ± 5 %) and during the first hour post-rotation (from 56 ± 3 to 41 ± 9 %); iii) fall in the brain temperature (from 37.1 ± 0.1 to $36.0\pm0.1^{\circ}\text{C}$); iv) reduction in heart rate (from 375 ± 6 to 327 ± 7 bpm); arterial pressure was not affected. Ondansetron, a 5-HT₃ antagonist, had no major effect on all observed parameters during both baseline and provocative motion. We conclude that in rats, provocative motion causes prolonged arousing effects, however without evidence of sympathetic activation that usually accompanies heightened arousal. Motion-induced fall in the brain temperature complements and extends our previous observations in rats, and suggests that, similar to humans, provocative motion triggers coordinated thermoregulatory response leading to hypothermia in this species.

Key words: provocative motion, motion sickness, sleep, brain temperature, cardiovascular.

INTRODUCTION

Motion sickness is one of the least studied and least understood biological phenomena. One of the reasons for this is that cardinal symptoms of motion sickness in humans – gastric awareness, nausea, facial pallor and cold sweating – could not be assessed in experimental animals.

Furthermore, the ability to vomit is absent in most commonly experimental species, rats and mice; motion sickness-induced retching and vomiting could be studied and has been reported in dogs, cats and musk shrews, e.g. (Noble 1948; Suri et al. 1979; Ueno et al. 1988). It is now however becoming recognized that nausea and vomiting represent totally different entities, both from the point of view of their pathophysiology and pharmacotherapy (Di Maio et al. 2013; Navari 2013). Indeed, while brainstem and peripheral mechanisms of emesis are relatively well understood (see (Hornby 2001; Sanger and Andrews 2006) for reviews), neural substrate of nausea is still unknown. Thus, retching and vomiting which could be quantified in animals possessing emetic reflex seem to be of limited utility for assessing nausea in general and motion sickness-induced nausea in particular. The only established biochemical marker of nausea in humans, elevated plasma vasopressin (Rowe et al. 1979; Fisher et al. 1982) has been confirmed in cats (Fox et al. 1987) and ferrets (Hawthorn et al. 1988) but not in rats (Rowe et al. 1979; Verbalis et al. 1986). Consequently, rodent studies of motion sickness-induced nausea have to rely on indirect indices, often with poor temporal resolution (eg. locomotor activity, food consumption) or limited face validity (eg. pica) that, in addition, is species-specific (Yamamoto et al. 2004; Liu et al. 2005). An efficient alternative to study motion sickness in rodents is using conditioned aversive paradigms, but this obviously requires time-consuming conditioning.

It is less known, but well documented that in humans motion sickness is associated with disturbed thermoregulation resulting in hypothermia in cold (Nobel et al. 2006; Cheung et al. 2011) and even in thermoneutral environment (Nobel et al. 2012). We have recently presented a preliminary report that a similar phenomenon is present both in rats and musk shrews: when animals of either species were subjected to provocative motion, their core body temperature fell, and these hypothermic responses were at least in part mediated by dilatation in cutaneous (tail) vascular bed leading to heat dissipation (Ngampramuan et al. 2013b) Neural mechanisms of motion sickness-elicited hypothermia are entirely unknown, and their evaluation seems to be a promising approach for revealing the neural substrate of nausea in general. We hypothesized that hypothermic responses might be triggered if provocative visual or vestibular stimuli somehow cause an increase in temperature in the preoptic hypothalamic area, where central thermosensitive neurons are located (Romanovsky 2007; Morrison and Nakamura 2011). To test

this hypothesis, we measured hypothalamic temperature (T_{hyp}) in a group of rats subjected to the same provocative motion protocol as was used in our previous study (Ngampramuan et al. 2013b).

Other symptoms of motion sickness in humans that were never examined in experimental animals are related to altered level of arousal - reduced alertness, lethargy and drowsiness, sometimes referred to as “sopite syndrome” (Graybiel and Knepton 1976). We considered that the most appropriate way to test whether provocative motion affects arousal in our rats would be to assess their wake/sleep pattern before, during and after stimulation. For this purpose, we recorded EEG and nuchal EMG for subsequent sleep staging. Lastly, we examined effects of provocative motion on heart rate and (HR) and blood pressure (BP) using biotelemetry, to test whether these cardiovascular measures have any potential for assessing nausea-like state in rodents. Here, combined instrumentation with EEG recording was advantageous as behavioural state (e.g. sleep/wake) affects autonomic control of the heart. Based on the human studies of motion sickness (Kim et al. 2005; Lacount et al. 2009; Kim et al. 2011), we expected mild or moderate tachycardia in response to provocative motion.

METHODS

Animals and preliminary surgery.

The experiments were performed with the approval of the Comitato Etico-Scientifico dell'Università di Bologna (Ethical-Scientific Committee of the University of Bologna), in accordance with the European Union Directive (86/609/EEC) and under the supervision of the Central Veterinary Service of the University of Bologna and the National Health Authority. All efforts were made to minimize the number of animals used and their pain and distress. Adult male Sprague Dawley rats ($n = 6$; Charles River Inc.) were anesthetized with a combination of diazepam (F. Hoffmann-La Roche), 5 mg/kg, i.m., followed by ketamine-HCl (Ketavet; Parke-Davis), 100 mg/kg, i.p. and placed in a stereotaxic apparatus (David Kopf Instruments) with the incisor bar set to keep the bregma and lambda on the same horizontal plane. Animals were surgically implanted with the following: (1) electrodes for EEG and nuchal electromyographic (EMG) recording; (2) a telemetric transmitter (PA-C40, Data Sciences International) placed intraperitoneally, with a catheter inserted into the femoral artery for the recording of arterial pressure (AP); (3) a thermistor (B10KA303N; Thermometrics) mounted inside a stainless-steel needle (21 gauge) was stereotaxically implanted above the left anterior hypothalamus to record the deep brain temperature (T_{hyp}). Stereotaxical coordinates for the thermistor were -1/0.5/-6.5 mm (AP/LL/DV) according to the rat brain atlas of (Paxinos and Watson

2007). All probes were secured to the skull with acrylic dental resin. After surgery, animals received 20 ml/kg saline subcutaneously and 1 μ l/g of Ampicillin (500mg/5ml) and 0,2 μ l/g of (Amicacin 500mg/10ml) intramuscularly. Animals recovered from surgery for at least 1 week in their home cages; they were kept at an ambient temperature of 24°C $\pm$ 0.5°C and under a 12 h light/dark cycle (light on at 09:00, 100 lux at cage level), and had access to food and water *ad libitum*.

Experimental design.

After recovery from surgery (1 week to 10 d), the experimental protocol consisted of four sessions conducted on different days, at least 72h apart: i) Ringer injection + rotation (Ringer/Spin condition), ii) Ringer injection (Ringer/No Spin condition); iii) Ondansetron injection + rotation (Onda/Spin condition); iv) Ondansetron injection (Onda/No Spin condition). Each session started at 10 a.m. and lasted for 6h. Each animal was exposed to all four protocols. The sequence of conditions were counter-balanced for every rat. . On the day of experiment, animals were adapted to the experimental cage (38 x 27 x 42 cm, L x W x H) located on a turntable. After this period animals received i.p. injection of either antiemetic ondansetron (0.5 mg/kg in 0.5 ml Ringer) or vehicle (0.5 ml Ringer). Thirty minutes later, the turntable was switched on, in the days of provocative motion, and rotation was maintained for 40 min at 33.3 rpm. During the non-rotation experimental session, home cages were left on a turntable for identical duration. In both instances, data collection was performed for another 3 h. At the end of the recording period, animals were returned to their home cages. The ambient temperature for the experiment was 20 $\pm$ 1°C. Ondansetron, a 5-HT₃ receptor antagonist, was from Sigma-Aldrich (USA); it's dosage was chosen according to (Tuerke et al. 2012).

Signal recording and data analysis.

The EEG, EMG, and T_{brain} signals were recorded by means of insulated copper wires connecting the headsocket to a swivel, amplified (Grass 7P511L; Astro-Med), filtered (EEG: high-pass 0.3 Hz, low-pass 30 Hz; EMG high-pass 100 Hz, low-pass 1 kHz; T_{hyp} high-pass 0.5 Hz), 12-bit digitalized (Micro MK 1401 III; CED; acquisition rate: EEG, 1 KHz; EMG, 1 KHz; T_{hyp}, 100 Hz), and stored on a digital hard drive. AP signal was telemetrically recorded, amplified, and digitally stored on a hard drive (acquisition rate: 500 Hz). Heart rate (HR) was derived from AP peak detection. Sleep stages were visually scored by an operator (1 s resolution), using the Spike 2 script *sleepscore*, freely downloadable from the CED website (www.ced.co.uk). Wake, NREM sleep, and REM sleep were scored according to standard criteria based on EEG, EMG, and T_{hyp} signals (Franken et al. 1991; Cerri et al. 2005). The time for the minimal duration of a wake–sleep episode was set at 4 s for Wake and 8 s for NREM sleep and REM sleep (Cerri et al. 2005).

Statistics:

Values are reported as mean $\pm$ SEM. Results were considered as independent groups for each post-injection time. A one-way ANOVA (SPSS 21.0) was used for the statistical analysis of the AP and HR during REM sleep results (due to the lack of REM sleep within the “Spin” conditions, see later in the text). A two-way ANOVA (SPSS 21.0) was used for the statistical analysis of all the other results. For the one-way ANOVA, the factor “Injection” was defined with two levels: Saline and Ondansetron. The modified t-test (t^*) was used for the pre-planned orthogonal contrast (Wallenstein et al. 1980; Winer et al. 1991): Saline vs. Ondansetron. For the two-way ANOVA analysis, the Main Factors were defined as follows: i) the factor “Injection” had 2 levels (Saline and Ondansetron); ii) the factor “Spinning Condition” had two levels (No Spin and Spin). The modified t-test (t^*) was used for both the pre-planned orthogonal and the pre-planned non-orthogonal contrasts (Wallenstein et al. 1980; Winer et al. 1991). The α level of the non-orthogonal contrasts was adjusted using the Bonferroni method. In particular, the following orthogonal contrasts were tested: Saline vs. Ondansetron, for each level of the factor Spinning Condition; and the following non-orthogonal contrasts were tested: no-Spin vs. Spin, for each level of the factor Injection. Since the time course of rotation-induced effects in cardiovascular parameters was quite variable, and since both AP and HR depends on sleep/wake state, we performed a 2-way ANOVA analysis, with experiment period (time) and sleep/wake stage as conditions. For all comparisons, statistical significance was set at $p < 0.05$.

RESULTS

Effects of provocative motion on sleep architecture.

Fig. 1 shows raw data traces, sleep staging and EEG spectrogram recorded in one rat before, during and after provocative motion following vehicle injection. EEG/EMG analysis revealed that REM sleep was totally abolished during the rotation period, and significantly reduced in the following hour, both in the Onda/Spin condition (first hour: 3.1 ± 1.1 % vs. 17.9 ± 4.6 ; $p < 0.05$ compared to not spin) and in the Ringer/Spin condition (first hour: 5.4 ± 1.5 % vs 20.4 ± 3.2 %; $p < 0.05$ compared to the not spin) as shown in Fig. 2 (bottom).

The time spent in NREM sleep was substantially reduced in both conditions with rotation (Onda/Spin: 6.6 ± 4.3 % vs. 55.4 ± 5.5 %; $p < 0.05$ compared to the Onda/No Spin; Ringer/Spin: 19.1 ± 5.5 % vs. 56.5 ± 6.1 %; $p < 0.05$ compare to the Ringer/No Spin) as shown in Fig. 2 (middle panel). In the first hour post-rotation, the amount of NREM sleep tended to be reduced in Ringer-treated rotated animals whereas for Ondansetron-treated animals there was no difference in this

value. In the second hour post-rotation, Ondansetron-treated and subjected to provocative motion animals had larger amount of NREM sleep ($64.0 \pm 2.4 \%$) compared to the three other conditions.

The amount of wakefulness was significantly increased during the rotation period compared to the non-spin conditions for both treatments (Ondansetron: $93.1 \pm 4.5 \%$ vs. $30.9 \pm 7.2 \%$; $p < 0.05$. Saline: $80.3 \pm 5.2 \%$ vs. $28.5 \pm 6.2 \%$; $p < 0.05$) (Fig. 2, top). In the first hour following rotation, the Ringer/Spin condition had a significant increase in the amount of wakefulness compared to the Ringer/No Spin ($52.4 \pm 11.0 \%$ vs. $21.8 \pm 2.6\%$, respectively; $p < 0.05$).

Effects of provocative motion on hypothalamic temperature.

Prior to the onset of rotation, the hypothalamic temperature was of $37.10 \pm 0.17^\circ\text{C}$, without differences between experimental sessions. In animals subjected to provocative motion, a noticeable fall in T_{hyp} could be seen within 5 min after the onset of rotation (Fig. 1); the temperature continued to drop until approximately 20 min of stimulation, then stabilized and slowly returned to the baseline within 1 h post-rotation. Overall, there was a significant fall in T_{hyp} during 40-min rotation, with a tendency for reduction during the 1st hour post rotation (Fig. 3). The timing and the magnitude of maximal fall in T_{hyp} did not differ between saline-treated and ondansetron-treated conditions ($-1.1 \pm 0.15^\circ\text{C}$ and $-1.2 \pm 0.10^\circ\text{C}$, respectively).

Effects of provocative motion on cardiovascular parameters.

Prior to the onset of rotation, HR was 373 ± 3 bpm, without differences between conditions. HR in awake state during rotation was significantly reduced compared to No Spin (Onda/Spin: 334 ± 4 bpm vs. Onda/No Spin: 376 ± 11 bpm, $p < 0.05$; Riger/Spin: 327 ± 7 bpm vs. Riger/No Spin: 375 ± 6 bpm, $p < 0.05$) (Figure 4, top). In the following hours, there were no differences of awake-state HR between the four experimental conditions.

During NREM sleep, there were no differences in HR values between the Spin and No Spin conditions, with both treatments (Fig. 4, middle). During the 1st hour post-rotation, HR in NREM sleep was significantly higher in the Onda/Spin (356 ± 18 bpm) compared to the Ringer/Spin condition (329 ± 7 bpm, $p < 0.05$). In the same time window, HR in the Onda/Spin condition was also significantly higher in REM sleep (379 ± 13 bpm) compared to the Ringer/Spin (340 ± 4 bpm; $p < 0.05$) (Fig. 4, bottom). HR values for REM sleep during rotation are absent as no REM sleep was detected during this time.

There were no differences between any experimental condition or their combination in the values of arterial pressure (Fig. 5).

DISCUSSION

The principal and novel findings of this work are that in rats, provocative motion causes substantial reduction in the brain (hypothalamic) temperature, provokes mild bradycardia and affects sleep architecture. In the subsequent discussion we address the relevance of these findings to the mechanisms of motion sickness, but initially we would like to provide the existing evidence that we employed a valid animal model of motion sickness. Firstly, in rats motion stimuli identical or similar to those used in the current study reduce locomotor activity (Ossenkopp et al. 1994) and food intake (Riccio and Thach 1968), an effects similar to non-specific symptoms of motion sickness in humans. More importantly however is that such stimuli also reliably increase pica (an unconventional consumption of kaolin caused by provocative motion) (Mitchell et al. 1977; McCaffrey 1985) and provoke conditioned taste aversion (Ossenkopp 1983), both being a recognised behavioural correlates of nausea in rats (Stern et al. 2011).

We believe that our most important observation is substantial ($\sim 1^{\circ}\text{C}$) reduction in the brain temperature during provocative motion. We argue that this fall is physiologically meaningful as it is only slightly smaller than reported values for circadian oscillations in T_{hyp} in free behaving rats (Shido et al. 1994; Gao et al. 1995) and is comparable to the amplitude of ultradian oscillations (Ootsuka et al. 2009). Current findings clearly demonstrate that our recently reported effects of provocative motion in rats – a fall in the peritoneal temperature associated with vasodilatation in thermoregulatory tail vascular bed (Ngampramuan et al. 2013b) - were not secondary to motion-induced rise in brain temperature as we initially hypothesized. It appears that the situation is rather opposite, so that the brain temperature falls together with peritoneal temperature due to, at least in part, an increase of heat dissipation via the skin of the tail. Of major interest are the facts that the time courses of motion-induced falls in brain temperature reported here and peritoneal temperature found earlier are quite similar, with sustained reduction extending well beyond the end of rotation, whereas tail warming/vasodilatation is transient – peaking at 20 min and then starting to return back (Ngampramuan et al. 2013b). This may indicate that in addition to an increase in heat dissipation, provocative motion also reduces thermogenesis; further clarification of this question would require separate experiments with recording of the temperature in the brown adipose tissue – a source of non-shivering thermogenesis. Lack of effect of ondansetron on motion-induced falls in T_{hyp} indicates that 5-HT₃ receptors are not involved in this response. At the same dose, ondansetron

prevents both conditioned and unconditioned responses to LiCl, a potent emetic substance (Tuerke et al. 2012; Ngampramuan et al. 2013a). It is thus most likely that in rats, motion-induced symptoms are resistant to ondansetron, similar to humans (Hershkovitz et al. 2009).

It now appears that in rats, provocative motion causes coordinated thermoregulatory response aiming to reduce body temperature. This is remarkably similar to what happens in humans experiencing motion sickness: sweating, reduction of thermogenesis, skin vasodilation in the limbs, behavioural preference for cooler environment – all leading to mild hypothermia (Cheung and Hofer 2001; Nobel et al. 2006; Cheung et al. 2011; Nobel et al. 2012). An obvious question that now arises is whether this (patho)physiological reaction is adaptive, and if so, what is its purpose. Here we share Ossenkopp's view (Ossenkopp et al. 1994) who suggested, based on the idea that hypothermia could represent a defence mechanism against intoxication, and on Treisman's theory that aversive sensation of nausea which accompanies motion sickness is a by-product of evolutionary developed defence against ingested neurotoxins (Treisman 1977), that motion sickness-induced hypothermia is a manifestation of this evolutionary beneficial reaction.

The amount of sleep was dramatically reduced during provocative motion. This is not surprising providing rotation was a novel sensory experience for our subjects, and like any stressor, likely had arousing effect. What is surprising and new is that prolonged wakefulness was accompanied by the *reduction* in HR when compared to awake state in non-rotated animals. In rats, most of environmental stressors cause tachycardia, with the only exception being the orienting response (Sanwald et al. 1970; Rockstroh et al. 1987). In the latter case, however, bradycardia is transient and short-lasting (seconds), and quickly habituate. Thus it is unlikely that central mechanisms involved in cardiac control during orienting response were responsible for sustained falls in HR reported here. It may be that the bradycardia was the consequence of vestibular stimulation, but this is again unlikely based on the fact that activation of vestibulo-sympathetic reflex (by direct electrical stimulation of vestibular afferents) causes depressor responses, with minor changes in HR (Ishikawa and Miyazawa 1980; Kerman et al. 2000). It thus appears that the bradycardia during rotation could be the result of descending influences from supra-medullary neural processes involved in integration of inputs from the vestibular afferents. This idea is indirectly supported by our observation that the effects of provocative motion on HR were state-dependent and disappeared when animals fell asleep during rotation. Our data do not allow to conclude whether these influences were mediated via withdrawal of cardiac sympathetic tone or via cardiac vagal activation.

Effects of provocative motion in cardiovascular parameters has never been examined in non-primate species, but were extensively studied in humans. The consensus of these studies is that the effects on the AP are absent (summarized by (Stern et al. 2011)), and this is in agreement with our finding. As for the effects on HR, provocative vestibular or visual stimulation in humans had either no effects (Graybiel and Lackner 1980; Sunahara et al. 1987; Hu et al. 1991; Cheung and Hofer 2001) or provoked mild tachycardia (Kim et al. 2005; Lacount et al. 2009; Kim et al. 2011), contrasting our observation in rats. In further rat studies, it would be most interesting to determine whether physical emetogenic stimuli affects heart rate variability indices as in humans such stimulation causes a marked reduction in the vagally-mediated HRV component (Hu et al. 1991; Lacount et al. 2009; Kim et al. 2011).

Effects of provocative motion on sleep architecture were prolonged, extending for at least 1h post-rotation. These our data indicate that REM sleep was affected more potently compared to NREM sleep. The mechanisms of these prolonged effects are currently unknown. Two early feline studies reported that integrity of medullary vestibular nuclei is essential for occurrence of normal REM episodes (Pompeiano and Morrison 1965; Perenin et al. 1972). These observations allow us to suggest that provocative motion affected REM sleep in our rats by altering normal functioning of vestibular system. Lastly, we found that reduction in NREM, but not in REM sleep was sensitive to ondansetron, suggesting selective involvement of 5-HT₃ receptors in this reduction. There are very few reports describing effects of vestibular stimulation on sleep in humans. In one such study, mild bed motion during the night had no major effects on sleep architecture (Woodward et al. 1990); likewise, galvanic vestibular stimulation was without effect on sleep latency at night (Krystal et al. 2010). In contrast, gentle rocking movements facilitated sleep onset and increased phase 2 sleep during short day nap (Bayer et al. 2011). Overall, it appears that arousing effects that we found in our rats contrast these human results. We believe however that this controversy is apparent, as sleep disturbances were reported in ship crew members, with a a strong link between sheep motion and these disturbances (Haward et al. 2009). It thus appears that our rat model resembles the latter situation.

In conclusion, in rats provocative motion causes prolonged arousing effect, however without evidence of sympathetic activation that usually accompanies heightened arousal or stress. Motion-induced fall in the brain temperature complements and extends our previous observations indicating that in rats, provocative motion triggers coordinated thermoregulatory response leading to

hypothermia. Providing striking similarities in the disturbances in thermoregulation induced by provocative motion in humans and rats, it is not unreasonable to speculate that in humans, as in rats, motion sickness could also cause a fall in the temperature of the brain, possibly contributing to accompanying lethargy and drowsiness.

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FIGURE LEGENDS

Fig. 1. Example of recording from one rat. The first vertical dashed line indicates the moment of the injection (ondansetron in this case), the second one indicates the beginning of spinning period and the third one - the end of spinning. Traces (from top to bottom): heart rate (HR), arterial pressure (AP), hypothalamic temperature (Thy), nuchal electromyogram (EMG), EEG spectrogram (EEG). In hypnogram, empty areas correspond to Wake, blue bars – to NREM sleep, and green bars – to REM sleep. Diastolic AP during rotation could not be seen at this compressed time scale due to multiple rotation-induced artefacts in the telemetric signal). In EEG spectrogram, spectral power is color-coded (from blue corresponding to low power and red corresponding to high power). Time of the day is shown below the horizontal axis.

Fig. 2. Average amount of wake, NREM sleep (NREMS) and REM sleep (REMS) (expressed as the percentage of each epoch) during the experiment for each experimental situation. Vertical dashed line divides the 40-min spinning period in the Ringer+Spinning and Ondansetron+Spinning experimental groups (and that of the corresponding time period in matched controls) from the following 60-min period. Data are shown as mean $\pm$ SEM. * = $p < 0.05$.

Fig. 3. Mean values for hypothalamic temperature (Thy) during wake, NREM sleep (NREMS) and REM sleep (REMS) during the experiment for each experimental condition. Vertical dashed line divides 40-min spinning period in the Ringer+Spinning and Ondansetron+Spinning experimental groups (and that of the corresponding time period in matched controls) from the following 60-min period. Data are shown as mean $\pm$ SEM. * = $p < 0.05$.

Fig. 4. Mean values for heart rate (HR) during wake, NREM sleep (NREMS) and REM sleep (REMS) during the experiment for each experimental condition. Vertical dashed line divides 40-min spinning period in the Ringer+Spinning and Ondansetron+Spinning experimental groups (and that of the corresponding time period in matched controls) from the following 60-min period. Data from REM sleep during spinning are absent as there was no REM sleep during this period. Data are shown as mean $\pm$ SEM. * = $p < 0.05$.

Fig. 5. Mean values for systolic arterial pressure (SAP) during wakefulness, NREM sleep and REM sleep during the experiment for each experimental group. Vertical dashed line divides 40-min spinning period in the Ringer+Spinning and Ondansetron+Spinning experimental groups (and that of the corresponding time period in matched controls) from the following 60-min period. Data from

REM sleep during spinning are absent as there was no REM sleep during this period. Data are shown as mean $\pm$ SEM. * = $p < 0.05$.