Phenotypic differences in the hemodynamic response during REM sleep in six strains of inbred mice

MATTHEW J. CAMPEN, YUGO TAGAITO, TODD P. JENKINS, PHILIP L. SMITH, ALAN R. SCHWARTZ, and CHRISTOPHER P. O’DONNELL. Phenotypic differences in the hemodynamic response during REM sleep in six strains of inbred mice. Physiol Genomics 11: 227–234, 2002. First published October 1, 2002; 10.1152/physiolgenomics.00031.2002.—The pattern of cardiovascular changes that occur at nighttime can have an impact on morbidity and mortality. Rapid-eye-movement (REM) sleep, in particular, represents a period of increased risk due to marked cardiovascular instability. We hypothesized that genetic differences between inbred strains of mice would affect the phenotypic expression of cardiovascular responses that occur in REM sleep. We monitored polysomnography and arterial blood pressure (P SA) simultaneously in six inbred strains of mice as they naturally cycled through sleep/wake states. Two strains elevated their P SA above non-REM (NREM) levels for 57.9 ± 6.6% (BALB/cJ) and 51.8 ± 8.4% (DBA/2J) of the REM period and exhibited a significant (P < 0.05) number of P SA surges greater than 10 mmHg (0.78 ± 0.36 surges/min for BALB/cJ; 0.63 ± 0.13 surges/min for DBA/2J). Despite similar P SA responses, the DBA/2J strain exhibited a decreased heart rate and the BALB/cJ strain exhibited an increased heart rate during REM sleep. The four other strains (A/J, C57BL/6J, C3H/HeJ, and CBAJ) exhibited a significant hypotensive response associated with no change in heart rate in three of the strains and a significant decrease in heart rate in the A/J strain. The overall variability in P SA during REM sleep was significantly greater in the C3H/HeJ strain (26.8 ± 2.0 mmHg; P < 0.0125) compared with the other five strains. We conclude that genetic background contributes to the magnitude, variability, and arterial baroreceptor buffering capacity of cardiovascular responses during REM sleep.

artrial baroreceptors; autonomic function; genetic; heart rate; heart rate variability; non-rapid-eye-movement sleep; sympathetic nerve activity; systemic arterial blood pressure

THE REGULATION of systemic arterial pressure (P SA) is markedly different between sleep stages. The transition from wakefulness to non-rapid-eye-movement (NREM) sleep is accompanied by an overall reduction in autonomic functions including metabolism, ventilation, heart rate, and P SA (2, 14, 16). In the transition from NREM to REM sleep, however, autonomic activity is distinctly variable, causing ventilation, heart rate, and P SA to become highly labile, potentially uncoupling blood supply from metabolic needs (5, 14, 16, 20). As such, REM sleep represents a period of increased cardiovascular vulnerability (19).

The variability of autonomic function during REM sleep makes it difficult to define a “normal” P SA response. In humans, REM sleep appears to cause an erratic but overall unchanged or increased P SA (2, 5, 16). This human profile of P SA change in REM sleep has also been reported in studies on rats and cats (9, 11, 13). In contrast, we have shown that dogs (8) and C57BL/6J mice (7) exhibit a distinct and repeatable hypotension during REM sleep, a response also seen in other studies using cats (4) and pigs (21). Many potential factors could contribute to these seemingly disparate findings between studies and species, including time spent in phasic vs. tonic REM sleep (10, 16) and baroreceptor buffering capacity (12). Moreover, it is possible that genetic factors affect the neural activity or peripheral vascular responses that occur during REM sleep and, therefore, account for the previously reported variation in P SA responses.

To date, there has been no systematic investigation of whether genetic factors influence the phenotypic expression of P SA responses during REM sleep. We have previously developed techniques to simultaneously record polysomnography and P SA in chronically instrumented C57BL/6J mice during REM sleep (7). Therefore, the purpose of the current study was to extend these initial observations from a single strain and compare P SA and heart rate responses during REM sleep in six common inbred strains of mice. We hypothesized that genetic differences between inbred strains of mice would affect the phenotypic expression of cardiovascular responses that occur in REM sleep.

METHODS

Surgical Procedures

Experiments were performed in 52 adult, male mice (12–16 wk old; Jackson Laboratories, Bar Harbor, ME). The animals were housed at the Johns Hopkins University in an
antigen-free and virus-free facility and subjected to a 12-h light (0900–2100) and 12-h dark cycle. Temperature and humidity were carefully monitored and maintained between 21–24°C and 30–60%, respectively. Food and water were available ad libitum throughout the study. A total of 6–12 animals were studied from each of the following strains in random order: A/J, BALB/cJ, C57BL/6J, DBA/2J, C3H/HeJ, and CBA/J. Two separate surgeries were performed on each animal. Anesthesia was induced and maintained using isoflurane administered through a face mask.

In the first surgery the mice were instrumented with chronically implanted polysomnographic electrodes for determination of sleep/wake state, as previously described (7). To describe in brief, a midline incision was made to expose the skull and muscles immediately posterior to the skull. Four electroencephalographic (EEG) electrodes and two nuchal electromyographic electrodes (EMG) were fashioned from Teflon-coated stainless steel wire (outside diameter 0.018 cm Teflon coated and 0.013 cm bare; A-M Systems, Everett, WA). The EEG electrodes were inserted into four predrilled holes in the frontal and parietal regions and bonded to the dorsal surface of the skull with dental acrylic (Land Dental, Wheeling, IL). The two EMG electrodes were stitched flat onto the surface of the muscle immediately posterior to the dorsal area of the mouse skull (EMG). The skin overlying the skull and posterior muscles was reapproximated, and the six electrodes exited the skin dorsally ~1.25 cm posterior to the point of EMG attachment. The total time from induction of anesthesia to recovery of consciousness was ~30–40 min. All animals were allowed 3–5 days to recover from the first surgery before undergoing the second surgery.

In the second surgery, an arterial catheter was chronically implanted in the left femoral artery for measurement of P\textsubscript{SA} (18). The femoral artery was exposed by a 1.5-cm cutaneous incision and blunt dissection of the fascia and surrounding connective tissue, then tied with 6-0 sutures distal to the point of catheter insertion. A 60-cm Renathane catheter (model MRE025; Braintree Scientific), heat-stretched and formed into a J-shape, was inserted with the aid of a 26-gauge needle and advanced ~0.5–1.0 cm toward the bifurcation of the aorta. The catheter was secured by suture and cyanoacrylate glue (Quicktite Superglue, Manco), then exteriorized at the base of the skull and secured to the EEG/EMG electrodes. The catheter was attached to a single-channel fluid swivel (model 375/25; Instech Laboratories) and perfused throughout the recovery and monitoring period by an infusion pump (model 375/25; Instech Laboratories) and perfused through an input control (7P5B; Grass Astronom, West Warwick, RI) and the arterial catheter connected to the pressure transducer. The length of the electrode-catheter unit allowed the animal to move freely within the cage during the data collection period.

**Experimental Protocol**

Experiments were conducted during the light cycle between 1200 and 1700 h in a quiet room. Each animal was permitted to acclimate for ~30 min before beginning data collection. The protocol consisted of allowing the mice to naturally cycle through their normal sleep/wake states for 3–4 h while polysomnography and P\textsubscript{SA} was continuously recorded.

**Data Analysis**

Sleep/wake states were assessed from continuous EEG and EMG recordings over 30-s epochs as described previously (7). Wakefulness was characterized by low-amplitude, high-frequency (~10–20 Hz) EEG waves and high levels of EMG activity compared with the sleep states. NREM sleep was characterized by high-amplitude, low-frequency (~2–5 Hz) EEG waves and an EMG activity considerably less than during wakefulness. REM sleep was characterized by low-amplitude, mixed frequency (~5–10 Hz) EEG waves, although the predominant pattern was a fixed amplitude theta frequency consistent with hippocampal theta rhythm. During REM sleep, the EMG activity was either equal to or less than that seen during NREM sleep, but always less than that seen during wakefulness. Two trained investigators conducted all sleep/wake state assessments manually; reproducibility of these methods has been confirmed previously (7).

The P\textsubscript{SA} and heart rate were analyzed for each period of REM sleep and compared with the corresponding mean values for the immediately preceding 120 s of NREM sleep. During each individual period of REM sleep the following parameters were determined: mean P\textsubscript{SA}; mean heart rate; maximum P\textsubscript{SA}; minimum P\textsubscript{SA}; percent of time in REM sleep that the P\textsubscript{SA} was above the mean value for the immediately preceding 120 s of NREM sleep; and number of P\textsubscript{SA} surges averaged over a consecutive 24-h period in six inbred strains of mice

<table>
<thead>
<tr>
<th>Strain</th>
<th>Mice per Group/Attempted Implantations</th>
<th>24-h P\textsubscript{SA}, mmHg</th>
<th>24-h HR, beats/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/J</td>
<td>8/10</td>
<td>88.4 ± 4.2</td>
<td>518 ± 70</td>
</tr>
<tr>
<td>BALB/cJ</td>
<td>10/18</td>
<td>98.9 ± 3.1</td>
<td>535 ± 25</td>
</tr>
<tr>
<td>C3H/HeJ</td>
<td>6/7</td>
<td>97.0 ± 1.4</td>
<td>670 ± 34</td>
</tr>
<tr>
<td>C57BL/6J</td>
<td>12/18</td>
<td>99.5 ± 2.4</td>
<td>564 ± 24</td>
</tr>
<tr>
<td>CBA/J</td>
<td>9/10</td>
<td>102.7 ± 2.6</td>
<td>676 ± 37</td>
</tr>
<tr>
<td>DBA/2J</td>
<td>7/8</td>
<td>89.4 ± 2.1</td>
<td>551 ± 61</td>
</tr>
</tbody>
</table>

Values are means ± SE. P\textsubscript{SA}, systemic arterial pressure; HR, heart rate. *strains with significant differences from other strains determined by Scheffe’s method, P < 0.05.

Quincy, (MA) was used to record EEG activity, EMG activity, and P\textsubscript{SA}; the arterial pulse rate was used to determine heart rate. Signals from the pen recorder were digitized at 300 Hz (DI-200 data acquisition board; Dataq Instruments, Akron, OH) and stored on optical disk with Windaq/200 acquisition software (Dataq Instruments).

Apparatus and Methods of Measurement

Arterial pressure measurements were made with pressure transducers (Cobe, Lakewood, CO) zeroed at midthoracic level. Calibrations were verified at the beginning and end of each experiment. A pen recorder (Grass Instruments, Quincy, MA) was used to record EEG activity, EMG activity, and P\textsubscript{SA}; the arterial pulse rate was used to determine heart rate. Signals from the pen recorder were digitized at 300 Hz (DI-200 data acquisition board; Dataq Instruments, Akron, OH) and stored on optical disk with Windaq/200 acquisition software (Dataq Instruments).

During data collection periods the animals remained in their single occupancy cages. The stripped ends of the polysomnographic electrodes were attached to the Grass polygraph via an input control (7P5B; Grass Astronom, West Warwick, RI) and the arterial catheter connected to the pressure transducer. The length of the electrode-catheter unit allowed the animal to move freely within the cage during the data collection period.
per minute greater than 10 mmHg above the mean value for the immediately preceding 120 s of NREM sleep. All \( P_{SA} \) measurements were determined from the digitally filtered \( P_{SA} \) signal (Windaq, filter factor 100, Dataq Instruments). The maximum and minimum \( P_{SA} \) were used to determine the overall variability of \( P_{SA} \) during REM sleep; percent of time in REM sleep that the \( P_{SA} \) was above NREM sleep levels and the number of \( P_{SA} \) surges per minute greater than 10 mmHg during REM sleep were used to determine the degree of hypertensive stress that occurred in REM sleep relative to NREM sleep. At the completion of the REM sleep protocol, monitoring was continued for a further 24-h period to establish baseline values for mean \( P_{SA} \) and heart rate for each of the six strains.

### Table 2. REM cycles, mean REM cycle duration, percent of the REM cycle period in which the \( P_{SA} \) is above preceding NREM level, and \( P_{SA} \) surges above the NREM level in six strains of inbred mice

<table>
<thead>
<tr>
<th>Strain</th>
<th>Mice per Group</th>
<th>REM Cycles per Mouse</th>
<th>REM Cycle Duration, s</th>
<th>( P_{SA} ) &gt; NREM, %</th>
<th>( P_{SA} ) Surges &gt; 10 mmHg per min REM</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/J</td>
<td>8</td>
<td>5.0 ± 0.8</td>
<td>78.3 ± 12.6</td>
<td>7.7 ± 4.1</td>
<td>0.07 ± 0.07</td>
</tr>
<tr>
<td>BALB/cJ</td>
<td>10</td>
<td>5.7 ± 1.0</td>
<td>62.9 ± 19.4</td>
<td>57.9 ± 6.6*</td>
<td>0.78 ± 0.36*</td>
</tr>
<tr>
<td>C3H/HeJ</td>
<td>6</td>
<td>9.2 ± 0.4</td>
<td>87.8 ± 18.2</td>
<td>17.8 ± 4.3</td>
<td>0.38 ± 0.11*</td>
</tr>
<tr>
<td>C57BL/6J</td>
<td>12</td>
<td>5.2 ± 0.7</td>
<td>76.4 ± 21.7</td>
<td>6.1 ± 1.6</td>
<td>0.01 ± 0.01</td>
</tr>
<tr>
<td>CBA/J</td>
<td>9</td>
<td>7.1 ± 1.8</td>
<td>69.4 ± 15.0</td>
<td>17.3 ± 4.7</td>
<td>0.01 ± 0.01</td>
</tr>
<tr>
<td>DBA/2J</td>
<td>7</td>
<td>4.8 ± 1.0</td>
<td>106.8 ± 14.5*</td>
<td>51.8 ± 8.4*</td>
<td>0.63 ± 0.13*</td>
</tr>
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</table>

Values are means ± SE. REM, rapid eye movement; NREM, non-REM. *significant differences between strains determined by the Scheffé method, \( P < 0.05 \).

Fig. 1. Representative tracings of arterial blood pressure (\( P_{SA} \)) responses during NREM and REM sleep in an A/J (top) and DBA/2J (bottom) mouse. At the onset of REM sleep, the \( P_{SA} \) of the A/J mouse decreases steadily from a mean of 96–84 mmHg. In contrast, the \( P_{SA} \) does not decrease and shows surges of 10 mmHg or more above NREM levels during REM sleep in the DBA/2J mouse. REM, rapid eye movement; NREM, non-REM.
Heart rate variability (HRV) was calculated from beat-to-beat intervals obtained by identifying systolic peaks of the arterial pressure waveform. The resulting tachograms (RR interval vs. time) were examined individually to detect and correct arrhythmias or artifactual values from the series. The tachogram was then transformed using a Lomb-type periodogram to determine the frequency spectrum (6) using a software program generated in collaboration the US Environmental Protection Agency and Dr. William P. Watkinson. This method was preferred over traditional Fourier analysis, as the Lomb-type transform is better suited for analyzing discrete data series as opposed to continuous, evenly sampled waveforms. The low-frequency range was calculated as the area under the curve from 0.02 to 1.5 Hz, and the high-frequency range was calculated between 1.5 Hz and the Nyquist frequency (heart rate frequency divided by two, typically between 4 and 5 Hz during sleep). As heart rate was not grossly different between sleep stages, no power normalization for greater frequency ranges was implemented.

Phenotypic measurements of PSA, heart rate, and HRV for each individual period of REM sleep were averaged for each mouse. A statistical difference in cardiovascular parameters between NREM and REM sleep was determined by paired t-test within each strain. One-way ANOVA was used to detect significant differences in change in PSA, change in heart rate, variability of PSA, percent time PSA was above NREM levels, and the duration of REM sleep between the six different strains. If the ANOVA was significant, then a post hoc test (Scheffe method) was used to identify which means were significantly different. Data are reported as means ± SE, and differences were considered significant if P < 0.025.

RESULTS

Baseline P<sub>SA</sub> and Heart Rate

Table 1 shows mean P<sub>SA</sub> and heart rate averaged over a continuous 24-h period in each of the six strains. The A/J and DBA/2J strains exhibited significantly lower P<sub>SA</sub> values, and the C3H/HeJ and CBA/J strains exhibited significantly higher heart rates, compared with the other strains.

Cardiovascular Changes During REM Sleep

REM sleep duration. The number of REM cycles ranged between 4.8 ± 1.0 and 9.2 ± 0.4 for the various mouse strains during the experimental period (Table 2). REM cycle duration lasted on average more than 60 s in all strains (range 62.9 ± 19.4 to 106.8 ± 14.5 s) but was of significantly longer duration in the DBA/2J strain compared with all other strains except the C3H/HeJ strain.

P<sub>SA</sub> and heart rate. Distinct patterns of cardiovascular behavior were observed between strains during REM sleep. Figure 1 is a sample tracing that illustrates contrasting cardiovascular responses exhibited by the A/J and DBA/2J strains during REM sleep. The A/J mouse (Fig. 1, top) develops a significant and sustained hypotension throughout the REM period. In contrast, the DBA/2J mouse shows a slightly elevated P<sub>SA</sub> during REM sleep, punctuated by short hypertensive surges above the preceding NREM levels.

The individual and mean changes in P<sub>SA</sub> and heart rate for each strain are shown in Figs. 2–4. The A/J, CBA/J, C3H/HeJ, and C57BL/6J strains all displayed significant hypotension during REM sleep (Fig. 2). The BALB/cJ and DBA/2J strains, however, maintained their P<sub>SA</sub> during REM sleep. When the change in P<sub>SA</sub> between NREM and REM sleep is plotted for each animal (Fig. 3, top), there is effectively no overlap in responses between the BALB/cJ and DBA/2J strains compared with the other four strains. The C3H/HeJ strain displayed the greatest lability in P<sub>SA</sub> of all six strains during REM sleep as determined by the maximum range of P<sub>SA</sub> fluctuation during REM sleep (i.e., maximum – minimum P<sub>SA</sub>; Fig. 3, bottom). Further evidence of the greater range of variability in P<sub>SA</sub> in the C3H/HeJ strain can be seen in the two right columns in Table 2. Despite the C3H/HeJ mice spending less than 20% of the REM period with the P<sub>SA</sub> above NREM levels, they still exhibited 0.38 ± 0.11 surges/min of greater than 10 mmHg above
NREM levels. In contrast, the CBA/J strain, which had a comparable period of time to the C3H/HeJ mice above NREM levels, exhibited no surges in P Sa.

The pattern of heart rate changes during REM sleep shown in Fig. 4 appears unrelated to the pattern of P Sa responses in the six strains described above (Fig. 2). Heart rate decreased significantly in the A/J and DBA/2J strains, increased in BALB/cJ strain, and displayed no significant trends in C57BL/6J, C3H/HeJ, and CBA/J strains.

Heart rate variability. No significant strain differences were observed with respect to baseline HRV values [high frequency (HF), low frequency (LF), or standard deviation of beat-to-beat intervals (SDNN)] during either NREM or REM sleep (Fig. 5) among the different strains. The change from NREM to REM sleep was associated with decreased high-frequency power (Fig. 5, top), a reported index of cardiac vagal activity, and increased low-frequency power (Fig. 5, middle), a reported index of cardiac sympathetic activity (1). SDNN values (Fig. 5, bottom) increased from NREM to REM sleep similar to the pattern seen for low-frequency power.

DISCUSSION

The current study presents a number of findings demonstrating that the phenotypic expression of P Sa and heart rate responses during REM sleep differ between inbred mouse strains. We report differences between strains in the overall change in P Sa during REM sleep (Figs. 2 and 3), the extremes of P Sa lability during REM sleep (Fig. 3), and the heart rate responses that accompanied changes in P Sa (Fig. 4). In the discussion that follows, we propose that genetic factors may in large part account for the variable P Sa responses previously reported during REM, and we examine potential neural pathways and neurotransmitters that regulate P Sa during REM sleep.
Pattern of P\textsubscript{SA} Responses During REM Sleep

At least three factors have previously been proposed to account for the diversity of P\textsubscript{SA} responses reported during REM sleep. First, the time of recovery after chronic instrumentation in animal studies may influence the pattern of P\textsubscript{SA} response seen during REM sleep. Early studies showed that chronically instrumented cats exhibited a marked hypotension and peripheral vasodilation during REM sleep (4). A more recent study in cats, however, demonstrated hypotension during REM sleep was restricted to the first few days after surgery (13). After more prolonged periods of recovery, REM sleep produced a hypertensive response that the authors (13) claim is similar to reports in other animals. Based on these data it could be concluded that under optimal conditions, neither humans nor animals exhibit a predominantly hypotensive response during REM sleep. However, in the context of the current study in which experiments were conducted within 2–5 days after surgery (13). After more prolonged periods of recovery, REM sleep produced a hypertensive response that the authors (13) claim is similar to reports in other animals.

Based on these data it could be concluded that under optimal conditions, neither humans nor animals exhibit a predominantly hypotensive response during REM sleep. However, in the context of the current study in which experiments were conducted within 2–5 days after surgery (13). After more prolonged periods of recovery, REM sleep produced a hypertensive response that the authors (13) claim is similar to reports in other animals. Based on these data it could be concluded that under optimal conditions, neither humans nor animals exhibit a predominantly hypotensive response during REM sleep. However, in the context of the current study in which experiments were conducted within 2–5 days after surgery (13). After more prolonged periods of recovery, REM sleep produced a hypertensive response that the authors (13) claim is similar to reports in other animals.

Second, studies in humans and animals have indicated that phasic REM periods, characterized by eye movements and pontogeniculocippitual (PGO) waves, are associated with surges in arterial P\textsubscript{SA} (10, 16). As such, the relative amount of time spent in phasic REM vs. tonic REM may influence the overall magnitude of the P\textsubscript{SA} response observed throughout a REM sleep period. In the current study, we did not measure eye movements or PGO waves, so we cannot exclude the possibility that the four strains of mice that exhibited a hypotensive response spent a greater proportion of their REM period in phasic REM than the two strains that did not exhibit hypotension. However, it should be noted that the C3H/HeJ strain, which produced an overall hypotensive response during REM sleep, exhibited the most labile P\textsubscript{SA} profile. Thus, at least in the C3H/HeJ strain, overall hypotension and heightened lability occur simultaneously, suggesting that if phasic REM accounts for the labile response, it was not sufficient to prevent hypotension. Future studies will be necessary to determine whether various inbred strains of mice display different proportions of tonic vs. phasic REM.

Third, baroreceptor buffering capacity may influence the P\textsubscript{SA} changes that occur during REM sleep. An early study in rats showed that baroreceptor denervation converted a previous hypertensive response during REM sleep to a hypotensive response (3). More recently, however, it has been reported that baroreceptor denervation accentuates the hypertensive response during REM sleep in rats (12). It is unclear what accounts for these opposite P\textsubscript{SA} responses during REM sleep after baroreceptor denervation. In our study, the relationship between P\textsubscript{SA} and heart rate varied between strains. Interestingly, heart rate changed in opposite directions during REM sleep in the DBA/2J and BALB/cJ strains, yet both strains similarly increased their P\textsubscript{SA} above NREM levels for more than 50% of the REM period and exhibited comparable surges in P\textsubscript{SA}. Furthermore, in the four strains that exhibited significant hypotension during REM sleep, there were no consistent changes in heart rate. Thus the absence of consistent heart rate changes to specific patterns of P\textsubscript{SA} response suggests that genetic background may influence baroreceptor buffering capacity during REM sleep in mice.

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![Pattern of P\textsubscript{SA} Responses During REM Sleep](image)
Neurotransmitters and Neural Pathways

A key neurotransmitter in the genesis of REM sleep and its associated cardiovascular response is acetylcholine. Carbachol, an acetylcholine agonist, can induce a REM-like state and cause an initial hypotension when injected into the pons. These findings led Shiromani et al. (15) to hypothesize that pontine muscarinic mechanisms trigger REM sleep and an associated hypotension. Furthermore, Shiromani et al. (15) suggested that with

Fig. 5. Heart rate variability (HRV) during NREM and REM sleep in six inbred strains of mice. High-frequency power is a marker for cardiac parasympathetic activity, low-frequency power is a marker for cardiac sympathetic activity, and the standard deviation of beat-to-beat intervals (SDNN) estimates overall variability of heart rate. Values are means ± SE. *Significant difference between NREM and REM sleep by paired t-test (P < 0.05).
increasing time in REM sleep, acetylcholine nicotinic receptors mediate a P_{SA} increase that overrides any muscarinic-induced decrease in P_{SA}. Thus, any genetic variation in nicotinic and muscarinic receptor distribution or function may influence the pattern and magnitude of P_{SA} responses that occur in REM sleep. Interestingly, a polymorphism in a neuronal acetylcholine nicotinic subunit has been reported in the DBA/2J mouse, but not in any of the other five strains we studied (17), suggesting the possibility that the P_{SA} response during REM sleep in the DBA/2J strain may be related to nicotinic receptor function.

The cardiovascular changes that occur in REM sleep are ultimately determined by autonomic output to the heart and vasculature. Previous studies in cats suggested that during REM sleep autonomic activity can vary between vascular beds, and, therefore, the P_{SA}, total peripheral resistance, and cardiac output changes during REM sleep will represent the sum of responses in all vascular beds (4). It is possible that the strain differences in cardiovascular responses during REM sleep we report result from a varying pattern of autonomic activity in specific vascular beds. Although our study did not assess autonomic activity to specific vascular beds, we did perform HRV analysis as a marker of cardiac autonomic activity. Our data, however, showed a similar pattern of response in all strains with a decrease in high-frequency power and an increase in low-frequency power from NREM to REM sleep, a pattern comparable to that reported in humans (1). Thus a genetic basis for differences in regional autonomic control of vascular activity during REM sleep remains to be determined.

Summary and Implications

The findings of the current study show that genetic background can have a significant impact on the phenotypic expression of cardiovascular responses during REM sleep. We propose that these data may, in part, explain the inability of previous studies to define a consistent cardiovascular pattern during REM sleep, even within a single species. Thus genetic background may render particular individuals more susceptible to adverse cardiovascular outcomes during REM sleep, particularly in the presence of a comorbid condition such as obstructive sleep apnea. For example, an individual with the highly labile P_{SA} profile of the C3H/HeJ strain and significant REM-related apnea may be at increased risk of ischemia if P_{SA} fell precipitously during hypoxic events and at increased risk of elevated afterload if P_{SA} rose precipitously during posthypoxic periods of arousal. A goal of future studies will be to determine what specific genetic profile predisposes to cardiovascular pathology during REM sleep.

We thank Jessica A. Wilson and Kathryn M. Soaper for superb technical assistance.

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