Noise-Enhanced Heart Rate and Sympathetic Nerve Responses to Oscillatory Lower Body Negative Pressure in Humans

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1Educational Physiology Laboratory, Graduate School of Education, The University of Tokyo, Tokyo 113-0033; 2Cardiology Division, Saiseikai Futsukaichi Hospital, Fukuoka 818-8516; and 3Research Institute of Angiocardiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan

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Hidaka, Ichiro, Shin-ichi Ando, Hideaki Shigematsu, Koji Sakai, Soko Setoguchi, Taku Seto, Yoshitaka Hirooka, Akira Takeshita, and Yoshiharu Yamamoto. Noise-enhanced heart rate and sympathetic nerve responses to oscillatory lower body negative pressure in humans. J Neurophysiol 86: 559–564, 2001. By injecting noise into the carotid sinus baroreceptors, we previously showed that heart rate (HR) responses to weak oscillatory tilt were enhanced via a mechanism known as “stochastic resonance.” It remains unclear, however, whether the same responses would be observed when using oscillatory lower body negative pressure (LBNP), which would unload the cardiopulmonary baroreceptors with physically negligible effects on the arterial system. Also, the vasomotor sympathetic activity directly controlling peripheral resistance against hypotensive stimuli was not observed. We therefore investigated the effects of weak (0 to approximately –10 mmHg) oscillatory (0.03 Hz) LBNP on HR and muscle sympathetic nerve activity (MSNA) while adding incremental noise to the carotid sinus baroreceptors via a pneumatic neck chamber. The signal-to-noise ratio of HR, cardiac interbeat interval, and total MSNA were all significantly improved by increasing noise intensity, while there was no significant change in the arterial blood pressure in synchronized with the oscillatory LBNP. We conclude that the stochastic resonance, affecting both HR and MSNA, results from the interaction of noise with the signal in the brain stem, where the neuronal inputs from the arterial and cardiopulmonary baroreceptors first come together in the nucleus tractus solitarius. Also, these results indicate that the noise could induce functional improvement in human blood pressure regulatory system in overcoming given hypotensive stimuli.

INTRODUCTION

The concept of stochastic resonance (SR) (Gammaitoni et al. 1998; Wiesenfeld and Moss 1995), wherein noise enhances the response of a nonlinear system to weak signals, may be the basis of a general mechanism for weak signal transmission in a variety of neuronal systems, possibly including the brain. For example, the sensitivity of sensory neurons to weak signals can be optimized by adding noise (Collins et al. 1996a; Cordo et al. 1996; Douglass et al. 1993; Levin and Miller 1996; Nozaki et al. 1999). Moreover, several recent studies have shown that the higher CNS is well able to utilize noise-enhanced sensory information: noise enhances human tactile sensation (Collins et al. 1996b; Richardson et al. 1998), human visual perception (Simonetto et al. 1997), and animal feeding behavior (Greenwood et al. 2000; Russell et al. 1999). Whether these functional improvements result from enhanced sensory afferent activity at the receptor level or from the effects of noise on the CNS is still unknown, however.

We recently demonstrated that noise could enhance the homeostatic function of the human blood pressure regulatory system (Hidaka et al. 2000). In that experiment, noise applied to the carotid sinus baroreceptors from outside enhanced the heart rate (HR) response to very weak changes in the central venous pressure induced by oscillatory tilt. Although earlier studies indicated that SR only affects receptor organs (Chiu-Tan et al. 1996; Collins et al. 1996a; Cordo et al. 1996; Douglass et al. 1993; Levin and Miller 1996; Nozaki et al. 1999), because carotid sinus and cardiopulmonary baroreceptor afferents, which respectively transmitted the information on noise and signal, first come together in the nucleus tractus solitarius, we suggested that SR exerts its functional effect by adding noise in the brain. We drew this conclusion with reservations, however, as oscillatory tilt inevitably perturbed hydrostatic blood pressure at the carotid sinus, and this small periodic signal may have thus been presented to the carotid sinus baroreceptors, which would support the notion that SR exerts its effect on the receptor organs.

In the present study, therefore we used weak oscillatory lower body negative pressure (LBNP) to inject a signal that affected the central venous pressure, but that had physically negligible effects on the arterial system, while we simultaneously added noise to carotid sinus baroreceptors.

The second aim of the present study was to examine whether vasomotor responsiveness would be enhanced by adding noise into the brain stem. The question is thought to be important because the enhanced vasomotor control for peripheral resistance has a stronger effect than HR in overcoming given hypotensive stimuli, and hence inducing the functional improvement in human blood pressure regulatory system. We measured muscle sympathetic nerve activity (MSNA) to investigate this possibility.

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Subjects

Eight male volunteers (ages 26.2 ± 3.9 yr, mean ± SD) participated in this study after providing written informed consent. All were healthy and took no medication. We were able to obtain good quality MSNA records from six of the eight subjects, which were then used for further analyses. This study was approved by the Human Research Committee, Research Institute of Angiocardiology, Kyushu University.

Experimental protocol

Each subject assumed a supine position on a bed, and his lower body was placed inside a cylindrical, airtight tank with a footrest. After attaching the various measuring devices to the subject, a single 40-min session was carried out in which periodic LBNPs and beat-by-beat random neck chamber pressures (NCPs) were provided to the baroreflex system as a signal and noise, respectively.

The human baroreflex system has the arterial and the cardiopulmonary baroreceptors of which the afferents are independently transmitted to a reflex center in the brain stem; from here the integrated outputs to peripheral organs such as the heart and the vascular system are sent via common efferent pathways (Andresen and Kunze 1994). We hypothesized that injection of noise into one receptor would enhance the response of the baroreflex system to a small signal added to the other receptor, and thus SR could occur in the baroreflex system via the interaction between signal and noise in the brain stem.

As a signal, we periodically unloaded the cardiopulmonary baroreceptors using oscillatory LBNP. The frequency of oscillation was fixed at 0.03 Hz, which is sufficiently slower than the neurally mediated baroreflex responses, and the oscillation amplitude was fixed at 0 to approximately −10 mmHg, with 0 mmHg corresponding to the atmospheric pressure. The LBNP tank was connected to a vacuum cleaner, and a power processor (VSCP-15-N, Tokyo Riko, Tokyo) was used to set the input AC voltage.

Noise was added to the carotid sinus baroreceptors by compressing or expanding a pneumatic neck chamber (Eckberg et al. 1975). The intrachamber pressure, controlled by positive (EP-11, Nagano Keiki, Tokyo, Japan) and negative pressure regulators (IT209-32, SMC, Tokyo, Japan), was regulated on a beat-by-beat basis to generate Gaussian white noise with zero mean gauge pressure. The response time of the regulators was 0.9 s, which was fast enough to randomly control beat-by-beat NCPs. Thus the bandwidth of the noise was from 0.0067 Hz to 1.3 Hz after the occurrence of the QRS complex (Cleveland 1979); the time constant of 0.1 s. The preamplified signal was routed to a loudspeaker and a storage oscilloscope to auditorily and visually discriminate MSNA from skin sympathetic (SSNA) or other nerve activities. MSNA has four specific properties (Fagius and Wallin 1980; Vallbo et al. 1979). 1) MSNA is observed synchronously with heartbeats with the relatively constant lag time (≈1.3 s after the occurrence of R wave), while other nerve activities have no pulse rhythmicity. 2) The amplitude and frequency of MSNA bursts are increased by the Valsalva maneuver. 3) MSNA responses are observed by tapping the innervating muscle, but not by touching the skin, which sensitizes SSNA. 4) Echo stimulation (clapping hands by examiners) has no effect on MSNA, while SSNA shows a marked response to the abrupt sound. The position of the electrode was adjusted so that the signal satisfied these four criteria.

The integrated MSNA signal was stored on a DAT recorder and analyzed off-line at a sampling frequency of 100 Hz. MSNA bursts were identified, and the amplitudes were obtained for each heartbeat. The amplitudes were converted to relative values by setting the maximum burst amplitude for each subject to 1,000 arbitrary unit (a.u.). To avoid subjectivity in detecting bursts by examiners, small bursts (<200 a.u.) were not used.

Data analyses

After removing noisy artifacts, 40-min RRI time series were interpolated and resampled using the cubic spline function to yield 4,096 (=212) data points, which were then used to convert the time series into an analytic signal and to evaluate the instantaneous signal-to-noise ratio (SNR) for the entire data set. After Hilbert transformation, time-frequency distributions (Wigner-Ville distributions) were calculated (Cohen 1989; Novak and Novak 1993) using a 256-point data window corresponding to 2.5 min. At each time point, a mean distribution value within a signal bandwidth (Δf = 0.025–0.035 Hz) was calculated. The noise component (Δn) within this distribution value was estimated by a geometric mean of the average distribution values just below (0.015–0.025 Hz) and above (0.035–0.045 Hz) the signal bandwidth. The geometric instead of an arithmetic mean was used here because the RRI time series in the low-frequency range has been shown to have a power law decay in the spectrum (Goldberger et al. 1990; Yamamoto and Hughson 1994). The SNR of the RRs (SNR RRI ) was then calculated by (ΔfΔn)/Δn. This temporally varying SNR RRI was further smoothed using the method of robust locally weighted regression (Cleveland 1979) to examine the transient responses in SNR RRI with increasing levels of noise.

Because of the inherently silent nature of MSNA during weak LBNP, continuous evaluation of the SNR as done for SNR RRI was impossible. We therefore divided the 40-min data into nonoverlapping 10-min segments (stages I, II, III, and IV) within which SNRs for the pooled MSNA bursts were evaluated; the mean SD of the noise at each stage was 0.66, 4.41, 11.91, and 23.16 mmHg, respectively. In addition, as the noise-induced bursts of MSNA were observed only when the LBNP was the lowest (Fig. 2B), we only used MSNA bursts within windows (period L) during which LBNP was lower than −8.555 ± 0.034 mmHg, corresponding to 80 percentile of heartbeats for each subject. For comparison, bursts occurring within windows (period H) during which LBNP was higher than −0.055 ± 0.003
mmHg, corresponding to 20 percentile of heartbeats, were collected from the same number of heartbeats as for period L.

The burst frequency (BF), mean burst amplitude (MBA), and the total nerve activity (TNA = BF × MBA) were calculated for each period (L or H) at each stage (I, II, III, or IV). We also calculated mean HR and SBP, after being band-pass filtered (0.01–0.05 Hz) (Hidaka et al. 2000), for each period at each stage. SNRs for BF (SNR_{BF}), MBA (SNR_{MBA}), TNA (SNR_{TNA}), HR (SNR_{HR}), and SBP (SNR_{SBP}) were obtained by dividing the values obtained from period L by those from period H.

Statistical analyses

Values are represented as means ± SD. Two-way ANOVA was performed to evaluate the effects of LBNP (L or H) and noise stage. One-way ANOVA was used to evaluate the effect of noise stage on SNRs. For multiple comparisons of the values at stages II, III, and IV with those at stage I, the paired t-test was used. Holm’s correction (Holm 1979) was applied to keep the total error of the tests below 5%. Values of P < 0.05 were considered significant.

RESULTS

Figure 1C shows a representative transient response of an RRI time series in one subject. As in our previous study (Hidaka et al. 2000), the RRI time series was band-pass filtered (0.01–0.05 Hz) to more clearly show the periodic oscillation induced by LBNP. This filtering procedure was not used in calculating SNR_{RRI}. The magnitude of the RRI oscillations evoked by the oscillatory LBNP (Fig. 1B) initially increased until reaching a maximum, and then gradually declined as the noise level continued to increase (Fig. 1A).

The voltage commands sent to the LBNP tank were sinusoidal, but due to the mechanical properties of the tank-processor system, the measured LBNP signal was not, although it was periodic (Fig. 2, A and B). However, as the RRI responses appeared locally sinusoidal compared with LBNP (Fig. 1B), we only used the first harmonic in calculating SNR_{RRI}. Consequently, in all six subjects, the transient changes in SNR_{RRI} were characterized by the bell-shaped curves typical of SR phenomena (Gammaitoni et al. 1998; Wiesenfeld and Moss 1995) (Fig. 1D).

Figure 2, A and B, shows representative MSNA records obtained from one subject at stages I and III, respectively. At stage I, MSNA bursts seemed to be distributed uniformly in time and were less related to LBNP. At stage III, by contrast, the bursts were more clustered within the period during which LBNP was the lowest. The arterial blood pressure recordings seemed to be well stable at both stages.

HR, SBP, and MSNA responses to LBNP at different stages of noise intensity are summarized in Table 1. Two-way ANOVA showed that BF and TNA in period L were significantly greater than those in period H. LBNP had no significant effect on HR, SBP, and MBA. While no significant effect of noise intensity (stages) was found by two-way ANOVA,
The rationale behind our probing SR within the baroreflex center in this and the previous study (Hidaka et al. 2000) is as follows. Earlier physiological studies showed that when decreases in LBNP (or increases in tilt angle) were small, and hence so were changes in central venous pressure (Johnson et al. 1974), the end-organ responses, including changes in HR (or RRI) and arterial blood pressure, were minimal. Greater LBNP or lower central venous pressure, by contrast, resulted in marked hemodynamic responses (Johnson et al. 1974). In other words, the curves describing the relationship between the cardiopulmonary baroreflex and central venous pressure were likely to exhibit threshold-like nonlinearity often associated with SR (Gammaitoni et al. 1998; Wiesenfeld and Moss 1995).

Thus without adding noise, weak changes in central venous blood pressure induced by oscillatory LBNP should not result in appreciable end-organ responses, which might in turn activate the arterial baroreflex.

On the other hand, the changes in carotid sinus pressure evoked by the neck chamber device are readily transmitted to the CNS, because in normal humans, arterial baroreflex responses to changes in the carotid sinus pressure are highly linear near the operating point (Mancia and Mark 1983). As this afferent noise is independently transmitted to the nucleus tractus solitarius in the brain stem (Andersen and Kunze 1994), where it merges with the signal from the cardiopulmonary baroreceptors, the effects of the noise, if present, would likely be indicative of SR within the brain.

Our findings that noise enhances SNR<sub>RR</sub> and SNR<sub>H</sub> are consistent with that scenario. Although we previously obtained similar results using weak oscillatory tilt (Hidaka et al. 2000), we had reservations because oscillatory tilt inevitably perturbs hydrostatic blood pressure at the carotid sinus, and a small periodic signal might thus be presented to the baroreceptors there. In addition, as the subject’s head moved periodically, the effect of the vestibular system on the baroreflex modulation of HR (Yates 1992) also complicated the interpretation. By minimizing these factors using oscillatory LBNP, we were able to show the functional benefits of added noise in the brain. In fact, we could not find any significant differences in SBP between periods L and H, and SNR<sub>SBP</sub> was not significantly altered by adding noise. This strongly suggests that we could minimize

differences in HR between periods H and L at stages II and III seemed to be greater than those at stages I and IV, suggesting that the HR response to weak LBNP was augmented by adding intermediate levels of noise. Consequently, multiple comparisons following one-way ANOVA showed that SNR<sub>H</sub> was significantly greater at stage II than at stage I (Table 1 and Fig. 3A). The noise response curves of SNR<sub>H</sub> (Fig. 3A) were very similar to the continuous SNR<sub>RRI</sub> calculated from the Wigner-Ville distribution (Fig. 1D). In SNR<sub>SBP</sub>, no significant difference was found between stages (Table 1 and Fig. 3B). Also, as mentioned above, SBP had no significant effect of LBNP, suggesting that there was no appreciable change in the arterial blood pressure and hence in the carotid sinus baroreceptor inputs in synchronized with oscillatory LBNP.

Although insignificant, SNR<sub>BF</sub> in general seemed to be improved at intermediate noise levels (Fig. 3C). There was no significant noise-dependent change in SNR<sub>MBA</sub> (Table 1 and Fig. 3D). When compared with stage I, SNR<sub>TNA</sub> at stage II seemed to increase slightly, and that at stage III was significantly greater (Table 1 and Fig. 3E).

**DISCUSSION**

The rationale behind our probing SR within the baroreflex center in this and the previous study (Hidaka et al. 2000) is as follows. Earlier physiological studies showed that when decreases in LBNP (or increases in tilt angle) were small, and hence so were changes in central venous pressure (Johnson et al. 1974), the end-organ responses, including changes in HR (or RRI) and arterial blood pressure, were minimal. Greater LBNP or lower central venous pressure, by contrast, resulted in marked hemodynamic responses (Johnson et al. 1974). In other words, the curves describing the relationship between the cardiopulmonary baroreflex and central venous pressure were likely to exhibit threshold-like nonlinearity often associated with SR (Gammaitoni et al. 1998; Wiesenfeld and Moss 1995).

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**TABLE 1.** Heart rate, systolic blood pressure, and muscle sympathetic nerve responses to LBNP and different stages of noise intensity

<table>
<thead>
<tr>
<th>Stage, mmHg</th>
<th>I (0.7)</th>
<th>II (4.4)</th>
<th>III (11.9)</th>
<th>IV (23.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>69.5 ± 17.4</td>
<td>70.1 ± 16.7</td>
<td>70.3 ± 17.6</td>
<td>69.2 ± 17.4</td>
</tr>
<tr>
<td>H</td>
<td>68.3 ± 15.9</td>
<td>67.6 ± 14.3</td>
<td>68.2 ± 15.7</td>
<td>68.2 ± 15.2</td>
</tr>
<tr>
<td>SNR*</td>
<td>1.01 ± 0.03</td>
<td>1.03 ± 0.04</td>
<td>1.03 ± 0.03</td>
<td>1.01 ± 0.04</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>123.8 ± 12.5</td>
<td>120.7 ± 12.4</td>
<td>120.7 ± 11.6</td>
<td>123.7 ± 9.1</td>
</tr>
<tr>
<td>BF, bursts/beat</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>0.33 ± 0.07</td>
<td>0.31 ± 0.10</td>
<td>0.34 ± 0.10</td>
<td>0.30 ± 0.06</td>
</tr>
<tr>
<td>H</td>
<td>0.20 ± 0.06</td>
<td>0.16 ± 0.05</td>
<td>0.19 ± 0.10</td>
<td>0.21 ± 0.10</td>
</tr>
<tr>
<td>SNR</td>
<td>1.68 ± 0.44</td>
<td>2.01 ± 0.82</td>
<td>2.05 ± 0.70</td>
<td>1.77 ± 0.75</td>
</tr>
<tr>
<td>MBA, ×10&lt;sup&gt;2&lt;/sup&gt; a.u.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>3.99 ± 0.53</td>
<td>4.05 ± 0.67</td>
<td>3.72 ± 0.52</td>
<td>3.78 ± 0.57</td>
</tr>
<tr>
<td>H</td>
<td>3.67 ± 0.24</td>
<td>3.90 ± 0.42</td>
<td>3.38 ± 0.20</td>
<td>3.75 ± 0.46</td>
</tr>
<tr>
<td>SNR</td>
<td>1.08 ± 0.10</td>
<td>1.03 ± 0.09</td>
<td>1.10 ± 0.13</td>
<td>1.01 ± 0.08</td>
</tr>
<tr>
<td>TNA, ×10&lt;sup&gt;2&lt;/sup&gt; a.u.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>181.3 ± 104.3</td>
<td>176.5 ± 106.0</td>
<td>172.4 ± 87.8</td>
<td>148.8 ± 52.7</td>
</tr>
<tr>
<td>H</td>
<td>107.7 ± 31.7</td>
<td>93.9 ± 32.8</td>
<td>83.4 ± 35.3</td>
<td>103.2 ± 42.6</td>
</tr>
<tr>
<td>SNR*</td>
<td>1.62 ± 0.53</td>
<td>1.80 ± 0.68</td>
<td>2.21 ± 0.87</td>
<td>1.65 ± 0.70</td>
</tr>
</tbody>
</table>

Values are means ± SD. LBNP, lower body negative pressure; HR, heart rate; SNR, signal-to-noise ratio; SBP, systolic blood pressure; BF, burst frequency; MBA, mean burst amplitude; TNA, total nerve activity. * P < 0.05 for main effect of noise. † P < 0.05 from stage I.
the factors described above. While noise-enhanced information processing in brain has been proposed based on observations of SR in a mammalian brain preparation (Gluckman et al. 1996; Stacey and Durand 2000) and with a dynamic model (Mandell and Selz 1993), the current findings provide the first experimental confirmation for a functional role of noise in the brain.

We also observed that noise enhanced SNR_{TNA} responses, which are directly related to the vasomotor responsiveness controlling peripheral resistance against hypotensive stimuli. However, the result was different from that for SNR_{BF} in that there was no significant increase in SNR_{TNA} at the earlier stage II (Fig. 3E). It is still unclear whether the relationship between LBNP and MSNA responses would exhibit apparent threshold-like nonlinearity. Jacobsen et al. (1993) measured MSNA while applying 5-min graded LBNPs of −5, −10, and −15 mmHg, and reported that both BF and TNA increased exponentially with increasing levels of LBNP. Zoller et al. (1972) also reported that forearm blood flow, reflecting peripheral sympathetic activity, decreased exponentially with application of LBNPs of −5, −10, −20, and −40 mmHg. These results indicate that the response curves for MSNA to LBNP have no obvious threshold, although they do possess threshold-like nonlinearity. The blunted MSNA responses to LBNP might thus result in the delayed SR curve for SNR_{TNA}.

There are some methodological limitations in the current study. First, the length of the period of data collection was limited to 40 min, mainly to limit the restrictive stress on the subjects, who were asked to maintain a constant waking state and a constant body position. A longer period of data collection might have enabled us to observe clearer SR effects, e.g., in SNR_{BF}. Second, a hysteresis or a time effect of monotonically increasing noise intensity might also be considered; however, this is unlikely, as we observed SR effects on RRI with a randomized design in terms of noise intensity (Hidaka et al. 2000).

In conclusion, we were able to confirm that SR is functionally operative within the human baroreflex center. We believe these results to be particularly important from the standpoint of baroreflex physiology. The current results suggest that simple evaluation of the linear transfer characteristics from the input (blood pressure) to the output (efferent neural activities and/or the target organ responses) (Kubota et al. 1992) may not be sufficient since noise intrinsic to the human cardiovascular system (Goldberger et al. 1990; Yamamoto and Hughson 1994) would alter the baroreflex sensitivity, i.e., the input-output relationship, even if the input stimuli were kept constant. This also suggests that the causality of the brain’s response might be influenced by the existence of background “noise,” and we might have to take the background fluctuations or ongoing (neural) activities into account when studying the regulatory systems in the brain.

We also believe the current observation on the enhancement of the brain stem responsiveness to be relevant as an experimental basis for a biomedical engineering application, whereby externally added noise is used to compensate for brain dysfunction such as orthostatic disorders, because the brain stem SR was obtained at a functional level in humans. Orthostatic intolerance affects an appreciable part of population (Robertson 1999), including the elderly (Lipsitz 1989), adolescents, and astronauts. The noise-induced sensitization of human baroreflex shown in this study may provide an alternative treatment strategy to traditional nonpharmacologic interventions such as salt loading and elastic stockings (Lipsitz 1989).

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REFERENCES


