SPECIAL REPORT

Baroreceptor stimulation alters cortical activity

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Abstract

The arterial baroreceptors constitute an essential sensory link for the short-term regulation of blood pressure and may also influence higher cortical function. The present study was undertaken to evaluate previous reports of such a cortical influence under conditions of psychologically controlled, mechanical baroreceptor stimulation. This control was achieved by use of PRES (phase-related external suction), a modified neck suction technique. PRES applies short suction bursts that have a different impact on baroreceptors depending on their timing within the cardiac cycle and has the advantage that subjects cannot easily discriminate between conditions of stimulation and inhibition. Electroencephalograms were recorded from 22 subjects during PRES manipulations. A surface-negative shift of about 10 μ V developed during the cuff manipulations. Over frontal-central regions, this shift was smaller during baroreceptor stimulation than during inhibition. These data provide support for the proposal that baroreceptor activation influences cortical activity.

Descriptors: Baroreceptor, Baroreceptor stimulation, Cortical potentials, Slow potentials, Interbeat interval, PRES

The homeostatic regulation of blood pressure is the main function of the baroreceptors (Kirchheim, 1976, Persson & Kirchheim, 1991). In addition to the regulation of blood pressure, baroreceptor activation seems to cause a global modulation of central nervous activity, and reduced arousal during baroreceptor activation has been observed by several investigators (e.g., Elbert et al., 1988; Elbert, Roberts, Lutzenberger, & Birbaumer, 1992; Koch, 1932; Rau et al., 1988; Vaitl & Gruppe, 1992). These effects of baroreceptor activation on cortical arousal have been studied using various baroreceptor manipulation techniques as well as various electroencephalogram (EEG) measures. For example, baroreceptor activity has been manipulated by body tilting (Vaitl & Gruppe, 1992) and by negative and positive air pressure in a cuff around the neck (Elbert et al., 1988; Rau et al., 1988). These studies suggest that baroreceptor activation causes a substantial reduction in slow cortical negative potentials, particularly the contingent negative variation (CNV), which is assumed to reflect cortical arousal (Birbaumer, Elbert, Canavan, & Rockstroh, 1990). Such a phenomenon would confirm that baroreceptor activity also modulates cortical mechanisms. How-

ever, in general the research has suffered from a lack of appropriate control conditions. Different degrees of body tilting, for instance, have a differential effect not only on the baroreceptors but also on a host of other receptors so that stimulation and inhibition conditions can be easily discriminated by the subjects. Similarly, different pressures in a cuff around the neck can be easily discriminated on the basis of the exteroceptive information, independent of actual baroreceptor stimulation condition.

Based on the neck suction method and an idea by Dworkin (1988), we developed a technique (Rau, Elbert, Geiger, & Lutzenberger, 1992) that allows the application of baroreceptor stimulation and inhibition conditions that are, at least at a group level, not reliably discriminable (Furedy, Rau, & Roberts, in press). Baroreceptors are stretch receptors that respond to extensions of the arterial wall. Any variance in pressure between the inside and the outside of the blood vessel will alter the firing rate of the baroreceptors. The receptors will not monitor whether such pressure changes have occurred inside or outside of the vessel. For the region of the carotid sinus, outside pressure can be manipulated noninvasively by a cuff around the neck. Our device relies on the application of short changes in cuff pressure temporarily related to different phases within the heart cycle (thus we refer to the technique as PRES: phase-related external suction). A brief external suction during systole has potent stimulatory effects on baroreceptors whereas the application of exactly the same pressure pulse during diastole disfacilitates the baroreceptor firing associated with the pulse wave because a negative pressure burst during systole adds to the pulse wave-

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triggered dilation of the vessel whereas the same suction burst during diastole will delay the recovery of the arterial stretch. To allow an ongoing period of stimulation, a sequence of alternating negative/positive pressure pulses is applied. In the stimulation condition, the electrocardiogram (ECG) R-wave triggers a negative pulse during systole that is followed by a positive one during diastole. In the control condition, this relationship is reversed.

In the present study, PRES was used to alter baroreceptor activity while slow brain potentials were recorded. Previous work using the neck suction technique (e.g., Rau et al., 1988) has shown that a slow negative shift develops during the trial. This shift might be an indicator of the subject's expectancy for the end of the trial. Surface negativity is modulated by "nonspecific" thalamocortical afferents. Cortical negativity results from depolarization of apical dendrites in the upper cortical layers, whereas cortical positivity may indicate disfacilitation of nonspecific thalamocortical activity (Birbaumer et al., 1990; Rockstroh, Elbert, Canavan, Lutzenberger, & Birbaumer, 1989). From the hypothesis that baroreceptor activation leads to dampening of cortical activation, it was postulated that the baroreceptor stimulation condition would reduce the amplitude of the surface negativity compared with that of the inhibition condition.

Method

Subjects

Subjects were 22 male University of Tübingen students of ages 20–29 years. Prior to participating in the study, all subjects were required to complete a health status questionnaire and to sign a consent form that summarized the experimental protocol. Exclusion criteria were cardiovascular, neurological, or psychiatric disorders. All subjects were paid DM 20 for participating in the study. The study's protocol was approved by the Ethical Committee of the Faculty of Clinical Medicine of the University of Tübingen.

Apparatus and Physiological Recordings

The ECG was measured through Beckman Ag/AgCl electrodes attached to the right clavicle and lower left rib cage. Electrode sites were cleaned with alcohol and rubbed with an abrasive jelly to improve contact. The R-wave of the ECG was detected by a Beckman cardiometer and fed to an IBM-AT compatible computer that measured the interval between successive R-waves to within ± 0.5 ms.

The EEG was measured with Ag/AgCl electrodes attached to the Fz, Cz, and Pz locations with a linked ear reference. Electrode resistance was kept below 5 k Ω . The EEG was amplified with a time constant of 30 s and a high-frequency cutoff set to 30 Hz. For the control of ocular artifacts, the vertical electro-oculogram was recorded from electrodes above and below the left eye. Trials with eye movement exceeding 70 μ V were excluded from the analysis. The amplified signals were fed into an analog-to-digital converter (Data Translation 2821) and converted with a sampling rate of 100 Hz. The digitized values were stored on hard disk for off-line analysis.

Carotid baroreceptors were stimulated by the method of Rau et al. (1992). Subjects were fitted with a neck cuff fashioned from lead and varnished to prevent contact with the skin. The edges of the cuff were padded with thick foam to ensure firm contact and user comfort. Pressure within the cuff was manipulated by a series of computer-controlled valves that were con-

nected to an air pump (vacuum cleaner). Pressure pulses of -30 mmHg and $+10$ mmHg were achieved by this equipment within 180 ms of valve operation. When baroreceptor stimulation was required, a negative pressure pulse was delivered at systole and a positive pulse at diastole within the cardiac cycle, whereas the reverse sequence was used when baroreceptors were to be inhibited. Systolic pulses (whether negative or positive) commenced 100 ms following detection of the cardiac R-wave. Their duration (t) was determined by the preceding interbeat intervals according to the formula $t = (M_p + M_g)/2 - 100$ ms, where M_p was the preceding cardiac interbeat interval and M_g was the mean of all interbeat intervals recorded up to that time in the experimental session. Diastolic pulses of the same duration of opposite pressure followed systolic pulses without delay (for further details using PRES, see Rau et al., 1992). The baroreceptors were stimulated or inhibited on successive cardiac interbeat intervals during trials of 6-s duration each.

Data acquisition, control of experimental stimuli, and baroreceptor manipulation were implemented by a computer program written in ASYST (Keithley/Metrabyte, Rochester, NY). Subjects were tested while seated upright in a sound-attenuated experiment room. Computers, polygraphs, and the air pump/valve assembly were located in the adjacent room.

Procedure

The whole experiment included 64 trials. Each trial consisted of a 1-s baseline period, and a 6-s baroreceptor manipulation phase, during which the cuff was activated. During every trial, weak electrical pain stimuli were delivered to the right index finger to evaluate effects of baroreceptor stimulation on pain perception. For the sake of brevity, these data are not reported here. The intertrial interval varied pseudorandomly between 12 and 19 s. Stimulation and inhibition trials were presented in a pseudorandomized order that was different for every subject. Subjects sat in a comfortable position in a reclining chair. They were instructed to stay alert and relaxed during the trials and to avoid eye movements.

Data Reduction and Statistics

Interbeat interval data were averaged across trials separately for conditions and subjects. On a second-by-second basis, data for a 1-s baseline and the 6-s trial were entered into an analysis of variance (ANOVA) with the repeated measurement variables of condition (baroreceptor stimulation vs. inhibition) and second (Seconds 0–5).

The slow cortical potential data were averaged across trials separately for conditions, electrode positions, and subjects. From these averages, change scores defined as differences between the baseline and stimulation periods (Seconds 1–5) were determined. The first second of the stimulation period (Second 0) was not parameterized because this interval is dominated by faster evoked responses. The difference scores were entered into an ANOVA containing the variables condition (baroreceptor stimulation vs. inhibition), second (Seconds 1–5), and electrode (Fz, Cz, Pz).

The ANOVAs were performed on a Apple Macintosh computer using the program SuperAnova (Abacus, Berkeley, CA). Significant effects were further examined by post hoc means comparisons. The p values for effects within variables with more than two levels (electrode and second) were corrected by the Greenhouse-Geisser procedure, and only the corrected p values are reported.

Results

Cardiovascular Responses

The observed interbeat interval changes confirmed the expected effect of the baroreceptor stimulation procedure (Figure 1). PRES stimulation caused a mean interbeat interval increase of about 43 ms, indicating that the desired baroreceptor activation was achieved. During the inhibition condition, however, mean interbeat interval dropped about 25 ms. The differential impact of the conditions is reflected in the condition ($F[1,21] = 107.6$, $p < .0001$) and Condition $\times$ Second effects ($F[6,126] = 43.1$, $p < .0001$, $\epsilon = .37$). As post hoc comparisons revealed, interbeat interval differences did not exist during the baseline ($F < 1$) and in the first second after the experimental manipulation ($F = 1$). However, within 2 s after the beginning of the pressure bursts, interbeat interval was significantly greater ($F = 64.1$, $p < .0001$) in response to the PRES stimulation as compared with the interval in the inhibition trials. The same was true (all F s > 154) for all subsequent seconds (2–5). Baseline interbeat interval was not significantly related to interbeat interval differences between inhibition and stimulation conditions ($r = .32$, $p > .15$).

Slow Brain Potentials

Figure 1 illustrates the time course of the averaged brain potential for the three electrode positions and the two experimental conditions separately. There was a significant electrode effect ($F[2,42] = 10.7$, $p < .001$) and post hoc tests revealed that negative shifts were more pronounced in amplitude over the frontal ($F = 14.9$, $p < .001$) and central ($F = 17.2$, $p < .001$) electrode than at Pz. Overall amplitudes did not differ between the central and frontal positions ($F < 1$). A significant interaction between condition and electrode ($F[2,42] = 4.3$, $p < .05$) was reflected by lower amplitudes for stimulation than for inhibition conditions at Fz ($F = 27.5$, $p < .0001$) and to a somewhat lesser degree at the vertex ($F = 8.1$, $p < .01$). At the Pz electrode, the difference between conditions was not significant ($p = .25$).

To examine the possibility that the magnitude of PRES cardiovascular effects was associated with PRES slow brain potential effects, correlational analyses between interbeat interval differentiation (stimulation value minus inhibition value) and slow brain potential differentiation (inhibition value minus stimulation value) were performed. Correlations for the frontal, central, and parietal positions were insignificant (all r s $< .23$, all p s $> .31$). Baseline interbeat interval was significantly associated with slow brain potential differentiation at Cz ($r = -.51$, $p < .02$) but not at Fz ($r = -.29$, $p > .2$) or Pz ($r = -.34$, $p > .1$).

Discussion

The present results support the claim that baroreceptor activation affects cortical activity. First, the effectiveness of the baroreceptor manipulation was evident in the interbeat interval increase (heart rate decrease) in response to stimulation and the decrease in response to inhibition. Although the PRES stimulation produced less pronounced heart rate decreases (9–10 vs. 3 beats per minute) than the continuous neck suction technique (Rau et al., 1988), the decreases were nevertheless highly significant. Furthermore, the PRES manipulation does not suffer from the problems associated with conventional neck suction techniques.

Figure 1. Upper panel: Mean interbeat interval responses to the stimulation (systolic negative and diastolic positive cuff pressure) and the inhibition (systolic positive and diastolic negative cuff pressure) condition. For technical reasons, interbeat interval data terminates with the cessation of cuff activation. Lower panels: Mean EEG responses to the PRES stimulation and inhibition conditions for the frontal, central, and parietal electrodes. Initiation and cessation of the 6-s cuff activation period as indicated by arrows (S on and S off).

Second, the slow negative shift that developed during PRES stimulation was modulated by the kind of manipulation; the shift was significantly smaller during stimulation, reflecting less cortical arousal (Birbaumer et al., 1990). Although this modulation was less than that observed in previous studies, the decrease was expected because of the less intense stimulation.

The modulation was evident frontally and centrally, but not parietally, in contrast to the report of Elbert, Tafil-Klawe, Rau, and Lutzenberger (1991). The small overall parietal amplitudes might be one explanation for this result. Also, PRES stimulation may differ not only in magnitude but also in quality from the continuous cuff pressure manipulation; the latter primarily activates the proportional aspect of baroreceptor firing, whereas the former relies primarily on the differential sensitivity of the receptors.

In the present experiment, we found no significant relation between PRES-induced cardiovascular differentiation and slow brain potential differentiation. Elbert et al. (1992) reported a significant negative relation: higher cardiovascular differentiation to lateral mechanical (not PRES) baroreceptor manipulation was related to less slow brain potential differentiation. That result suggests an inverse relationship between cardiovascular and cerebral baroreceptor responses, but the large percentage of subjects in that study who failed to display differentiation of heart rate but had large slow brain potential differentiation implies that the cortical responses may have been to the aver-

sive nature of the (readily discernable) stimuli and not to actual baroreceptor manipulation.

The present finding that baseline interbeat interval was negatively associated with central slow brain potential differentiation may be due to a combination of three factors. First, the shorter the interbeat interval, the greater the total number of suction intervals received. Second, there may be different effects of PRES as a function of interbeat interval. Third, if one assumes that faster heart rate is a sign of lability, then there is a consistency between cardiac lability and slow brain potential lability.

The generators of these slow potential shifts are difficult to determine from surface recordings alone. However, following the rationale of Braun, Lutzenberger, Miltner, and Elbert (1990) and Rockstroh et al. (1989), it seems quite likely that the observed shifts in brain potentials are generated cortically to a large degree. Although the overall amplitude changes must be widespread in origin, the difference between the conditions, being of the order of a few microvolts, might result from the activation difference of a relatively small area. To explain its extension across at least two electrode locations, the generator, if small in extension, must be relatively distant from the electrodes. A most likely explanation might be a differential activation of a region in the temporal lobe where baroreceptor projection areas are located (Ruggiero, Mraovitch, Granata, Anwar, & Reis, 1987).

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