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Rapid Auditory Evoked Vascular Response in Man

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Plethysmographic signals were recorded in four body regions (fingertip, forearm, cerebral cortex, and ophthalmic artery) of normal, healthy subjects during the presentation of brief auditory tones. Tones were presented during either systolic or diastolic phases of the cardiac cycle. Using data processing techniques similar to those employed in cortical evoked potential studies, averaged waveforms were derived which revealed the presence of a polyphasic volumetric response beginning as early as 150 ms (after onset of tones) in some subjects. Grand average waveforms suggested a similar morphology in all four body regions. The rapid onset argued for neural mediation of this response which may represent a sudden, transient flexure of vascular smooth muscle. The presence of this evoked vascular response in the brain suggests a previously unreported responsiveness of the cerebral vasculature in man to simple auditory stimulation. © 1985 Academic Press, Inc.

INTRODUCTION

The human nervous system is remarkably sensitive to brief auditory stimulation. Among the most reliable responses to unconditional stimuli are peripheral vasoconstriction, cephalic vasodilation, increased skin conductance, increased EMG activity, and alterations in heart rate. Some of these responses are obligatory reactions to exteroceptive stimulation which vary over repeated occurrences depending on their role in physiological adaptation processes. Sokolov (37) divided transient physiological responses to unconditional stimuli into three classes: the orienting, the adaptive, and the defensive. Orienting responses (ORs) are nonspecific and habituate quickly and adaptive responses (ARs) follow habituation of the OR and

Abbreviations: EVR—evoked vascular response; REG—rheoencephalography; AR, DR, OR—adaptive, defensive, orienting response.

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themselves do not habituate. Defensive responses (DRs) also appear after ORs habituate and occur in reaction to very intense or psychologically threatening stimuli. Sokolov distinguished DRs from ORs by differential responses of cutaneous vessels in the fingers and forehead.

In the case of plethysmographic responses, Cook (7) noted that auditory stimulation (95-dB, 1000-Hz tones) can induce changes in both blood volume and pulsatile amplitude, requiring 1.5 to 4 s to begin, peaking in 7 to 10 s with variable recovery times. These responses are believed to be mediated by the sympathetic nervous system. Of particular relevance to the present investigation are studies that showed rapid changes in brain electrical impedance variables in response to exteroceptive stimuli. Birzis and Tachibana (3) were the first to report a dynamic responsiveness of brain impedance plethysmographic (pulse volume) signals recorded from depth electrodes to various types of alerting stimuli in unrestrained cats. Tachibana *et al.* (38) reported similar phenomena in human surgical patients using implanted electrodes. Response latencies in these latter two studies were on the order of several seconds. Quantification and characterization of these stimulus-induced hemodynamic changes have not been accomplished, however, and consequently, their physiologic origins, and dynamic properties have remained uncertain.

METHODS

Volumetric responses of normal, healthy subjects in response to simple auditory tones were investigated employing stimulus presentation and averaging procedures borrowed from brain evoked potential studies (35, 36, 39, 40) in which it was found that auditory (tone) stimulation synchronized with the pulse pressure gradient (systolic, diastolic) exerted distinctive influences on evoked potential amplitude. Ten healthy, right-handed subjects were tested, five male and five female. The age range was 20 to 26 years and all were tested between 1300 and 1600 h. Plethysmographic signals were derived using two different volumetric techniques: photoplethysmography and electrical impedance plethysmography. Whereas photoplethysmographs detect only superficial (e.g., skin) vascular events, impedance-based signals reflect vascular events in deeper tissues as well (including all major arteries). Photoplethysmographic signals were recorded from the tip of the middle finger of the right hand and from the superficial opthalmic artery on the forehead. The sensors were secured in place with surgical tape. Electrical impedance waveforms were derived from placements on the left forearm and from the left central hemisphere of the cerebrum. On the arm, current-carrying bands (aluminum-backed Mylar) were placed approximately 3.8 cm above the wrist and 7.6 cm above the elbow with the

accompanying current-detecting pair placed approximately 10 cm apart and between the current pair.

To record intracranial volumetric ("plethysmographic") changes in normal human subjects, we applied a noninvasive electrical impedance measurement procedure known as rheoencephalography (REG). Although there have been some reports (28, 32) that the REG signal is substantially contaminated by scalp blood flow, these have been contradicted by a large body of literature indicating a cortical (i.e., intracranial) origin of the REG signals [reviewed in (16)]. For example, Jacquy *et al.* (19) found highly significant correlation of the REG method with an invasive radioisotope method in estimating regional cortical blood flow. Similarly, Hadjiev (16) found correlation of hemispheric flow values between the REG method and an isotope-based method (i.e., venous dilution). There are also several clinical reports which show that occlusion of the external carotid artery does not affect REG signals (21, 27, 34). Perhaps inappropriate REG techniques employed by some investigators are responsible for apparently conflicting results.

On the head, current-carrying electrodes (3×5 cm EKG-type electrodes overlying electrode gel-soaked cotton gauze squares) were placed along the midline on the forehead (between and just above the eyebrows) and over the occipital cortex, just above the inion. These were held in place with perforated, Velcro-adjustable latex bands. The current-detecting electrodes were standard Grass silver cups placed 7 cm apart on either side of C3 (10 to 20 electrode placement system) which overlies the left central cortex. Thus, two separate current-imposing and impedance-detecting circuits were applied in this study. Electrode gel used on all the forearm bands and electrodes on the head was a nondrying type (Marquette Electro-Creme). Electrode impedances from both placements were in the range of 20 to 40 Ω (at 100 kHz). Impedance signals were generated by a Minnesota Impedance Cardiograph (25, 26). These devices apply a 100-kHz sinusoidal current of 4 mA and output both basal impedance (Z_0) and the continuous change in Z_0 (ΔZ). Both electrical impedance signals (from head and forearm) as well as photoplethysmograph signals (fingertip and ophthalmic artery) were amplified and filtered at low frequency (time constant = 0.45 s) on a Grass Model 79 polygraph. Signals were collected on a PDP 11/34 computer at a sampling rate of 1 kHz for a period of 1256 ms, of which 256 ms was prestimulus and 1000 ms poststimulus.

To confirm that the REG procedure in the current study reflected intracranial pulse volume events, the effect of occluding scalp circulation was tested in a preliminary study of seven subjects. Scalp circulation was occluded using a thin pneumatic cuff (W. A. Baum Co., N.Y.) resulting in an average decrease of only 5% in peak amplitude in the averaged

waveforms (20 waves per average). Thus, the contribution of scalp blood flow is minimal with our procedure.

During the recording period, the arm was placed at heart level on a pillow with the subject sitting upright in a comfortable chair in a sound-dampened room with 15 dB white noise. Subjects were instructed to relax with their eyes closed during the experiment. There was no task assigned. Auditory stimuli were 450-Hz tones presented binaurally at 80 dB (SPL) for 200 ms through Sennheiser 424 headphones. Tone presentation and data collection epochs were triggered on either the systolic or diastolic phase of the cardiac cycle by a Schmidt trigger activated when the forehead photoplethysmographic waveform ascended to at least 75% of the maximum systolic peak height and descended to at least 25% of that height on the diastolic trough. Tones occurred randomly on systole or diastole, never on the same cardiac cycle, and were interspersed with homologous no-stimulus data collection epochs (both systolic and diastolic). Thus, data were collected under four conditions: stimulus-systole, stimulus-diastole, no-stimulus-systole, and no-stimulus-diastole for each of the four placements. The "no-stimulus" waves were those occurring just prior to a stimulus trial, for either condition.

To derive one averaged response, forty 1280-ms data epochs for each condition were collected and averaged in a manner identical to those used in previous brain evoked potential procedures (35, 36). Because body movements introduced artifacts into one or more of the plethysmographic signals, contaminated trials were automatically rejected by computer software. Each experiment required approximately 50 min. Prior to statistical analysis, the 1280 data points comprising each average waveform were themselves averaged at successive 20-point intervals to yield 64 data points.

RESULTS

To graphically illustrate stimulus-induced volumetric responses, difference waveforms for the simultaneously recorded head and forearm impedance signals were obtained by simple subtraction of stimulus from no-stimulus waveforms. For diastolic-synchronized stimulation, Fig. 1 shows clear polyphasic events for each subject with considerable intersubject variability. In some subjects, EVRs appeared to begin within 150 ms. For subjects 2 through 6, there was a striking similarity between vascular responses in the cortex and the forearm. In contrast, when the tone stimulation was synchronized with systole, there was relatively little evoked vascular activity in any of the four placements. Figure 2 compares diastolic- and systolic-synchronized difference waveforms for the cerebral REG.

Despite individual variation in EVRs, the grand mean difference waveforms exhibited EVRs of similar morphology for the two measurement

FIG. 1. Simultaneously derived evoked vascular responses (EVRs) for cerebral and forearm electrical impedance plethysmograms in eight subjects for diastole-synchronized stimulation. Vertical lines indicate onset of tone stimuli (during diastolic phase). Waveforms presented were obtained by subtracting stimulus from no-stimulus data epochs.

techniques. Thus, in Fig. 3, the impedance-derived EVRs (arm, head REGs) shared common features with the photoplethysmograph-derived EVRs (digital, cephalic). The downward peaks (dilation) in these waveforms were roughly 10% of the average peak amplitude for the arm and head REG and 7% for the digital and cephalic. Thus, the most consistent feature of the four EVRs was a transient vascular dilation, peaking in the range of 400 to 500 ms. A slight upward deflection appeared to precede this peak, being more pronounced in the impedance-derived signals. Little, if any response occurred during systole, although the cephalic (ophthalmic) placement showed a slight upward trend that returned to baseline before the end of the sampling period.

Figure 4 shows averaged pulse volume waves for a single subject for stimulus and no-stimulus conditions synchronized with diastole and systole.

FIG. 2. Comparison of difference waveforms for tone stimulation during diastole versus systole in cerebral rheoencephalography. Vertical calibration was 10% of maximum peak height of averaged pulse volume waveforms. Opposing waveforms were collected from the same subject.

Although there appeared to be some difference between the two conditions during systolic stimulation late in the sampling period, this could have been due to increased variability in the averages as the variance in the average

FIG. 3. Grand averages of individual subject's difference waves for all four placements.

increased from the point of time-locking (stimulus presentation). Note that in both conditions there was no difference between waveforms prior to tone presentation, indicating relatively stable prestimulus pulse-volume averages.

As no prior estimates of the EVR were known, several exploratory multivariate analyses were conducted. These descriptive statistics included a principal component factor analysis to define the structure of the EVR and jackknifed stepwise discriminant function analysis to discover the temporal focus of the differences between the stimulus and no-stimulus waves.

FIG. 4. Averaged pulse volume waves for one subject, showing effects of tone stimulation along the entire waveform. —, Prestimulus; ---, stimulus.

Four temporally adjacent factors of the REG record were identified with a varimax rotation of the factor structure generated by principal component analysis. The first factor consisted of the sampling epoch between 300 to 540 ms. The second (40 to 100 ms), third (100 to 200 ms), and fourth (200 to 300 ms) factors completed the description of the waveform.

The differences between the stimulus and no-stimulus pulse volume waves during diastole for the arm and head placements were analyzed by a four-way (condition $\times$ placement) stepwise discriminant function procedure (BMD P7M). A linear combination of variables occurring at 60, 140, 260, and 250 ms were selected as the most discriminating in this analysis. The stimulus and no-stimulus waves for the cortical REG record alone were discriminated for 62.5% of the cases (25% was chance). Analysis of the peripheral placement indicated that the stimulus and no-stimulus waves were separated 37.5 and 62.5%, respectively (not significantly different from chance which was 50% in this analysis).

However, separate two-way analysis of diastole-triggered EVRs for the REG record alone, yielded a very significant difference between the stimulus and no-stimulus waveforms. A total of 87.5% of the waves were classified accurately ($P < 0.05$). For the forearm, only 68% ($P > 0.05$) of stimulus and no-stimulus waves were classified accurately during the diastolic phase. By contrast, stimulation during systole was not significantly discriminated.

The "transit times" of the grand average pulse volume waveforms and corresponding difference waves (EVRs) were estimated by superimposing forearm and fingertip waves (Fig. 5). The peak latency differences (time at

FIG. 5. Above: Comparison of group average difference waves (EVRs) for forearm (---) and fingertip (—). Below; corresponding averaged pulse volume waves for forearm (---) and fingertip (···). Calibration marks: abscissa, 100 ms; ordinate, 10% change.

which peaks attained their maximum value) for averaged pulse-volume waveforms was approximately 60 ms and the latency difference for the most prominent component of the EVR in the difference waves was approximately 30 ms. No statistics were carried out on these data and they are presented only for visual inspection.

The temporal and structural variability in EVRs between individuals may reflect subject or procedural characteristics. Subsequent studies may confirm this variability. Procedurally, it could be caused by variability in the point during the cardiac cycle at which data collection/tone presentation is initiated. That is, the variability in the point at which the Schmidt trigger detects 75% amplitude as systole or diastole, will result in phase variance wave from one trial to the next. Consequently, successive data epochs may be slightly out of phase. Further, differences in heart rate (interbeat-interval) could create the appearance of a phase distortion. Further studies are required to evaluate these possibilities.

Our data do not allow any conclusions regarding net blood volume or blood flow changes. This is due to the fact that all signals were recorded with low-frequency filters to stabilize baselines and consequently, slow volume changes manifesting as sustained differences between stimulus and no-stimulus conditions may be filtered out. Also, data epochs spanned only 1 s (poststimulus) and thus trends of consistent flow change were not discernible.

DISCUSSION

As discussed in the Introduction, cardiovascular responses to external stimuli are not new in human neurophysiology. In the present investigation, however, we report an auditory evoked vascular response which occurs within the same cardiac cycle as the stimulus. The EVR had previously gone unobserved because it has such a short latency to onset and is relatively small compared with the amplitude of the pulse volume wave. A new approach to processing pulse volume waves was necessary to observe the EVR, namely, a phase-locked signal averaging technique borrowed from previous studies of the brain evoked potential (35, 36, 39, 40) provided the necessary reduction in signal-to-noise ratio without which individual EVRs would be undetectable.

The origin of the EVR is uncertain from this initial investigation although several possible mechanisms may be considered: (i) sudden flexure of the vascular smooth muscle resulting from direct neural influence through sympathetic efferent nerves, (ii) vagally mediated modulation of ventricular contraction, (iii) reflex activation of striate muscle. In the second case, an altered force or rate of contraction would manifest as a volumetric event

propagated through arterial pathways. Reflex activation of striate muscle in close proximity to major vessels seems possible in the limbs but cannot account for intracranial EVRs which in some subjects were isomorphic with EVRs in the arm. Of the first two possible mechanisms, our data seem to favor the first hypothesis because altered ventricular contraction would also result in identical latency differences between the forearm and fingertip EVRs and between peaks of the corresponding averaged pulse-volume waveforms (pulse transit time). This expectation is based on the fact that pulse-volume waves require a finite period of time to travel from the forearm to the finger. Thus, if the EVR were volume-propagated, its peak would have the same timing relationships as the peaks of the pulse pressure waves. It did not—the time between grand average pulse volume peaks for the forearm and the fingertip was approximately 60 ms (measured digitally) and the time between EVR peaks was 30 ms. Thus, the data in Fig. 5 argue for a direct effect of auditory stimuli (through brain stem-sympathetic efferent fibers) on the smooth muscle of the vessel walls, most likely, the arterioles. Although it might be proposed that a neural mechanism would produce simultaneous (peak) EVRs, some additional, finite time would be required for arrival of efferent nerve impulses at the vascular smooth muscle in the fingertip. Closer examination of these timing relationships is needed to definitely answer this question.

Perhaps the most salient feature of the EVR is its dependence on the phase of the cardiac cycle. Although two subjects showed a slight response during systole, it is clear from an inspection of the figures presented and the statistical analysis that the neural processes that generate the EVR are in some way "governed" by the cardiac cycle. The reason for this is not clear but might be related to previous findings of entrainment of sympathetic nerves to the cardiac cycle (6, 8, 17, 23) including muscle vasoconstrictor sympathetic neurons (15). Some investigators (1, 6, 14, 18) have proposed that increased baroreceptor nerve firing during systole, acting on brain stem vasomotor circuits, induces a delayed inhibition of sympathetic nerve discharge (with removal of inhibition and increased sympathetic discharge during diastole). However, more recent investigations by Gebber [reviewed in (12)] strongly indicated that brain stem vasomotor circuits themselves are the source of this entrainment. Thus, it seems likely that the neural activity responsible for the EVR is being modulated either in brain stem vasomotor centers or at the level of the sympathetic ganglia.

Gebber *et al.* (13), also conducted a series of experiments that may bear on the present data. They studied averaged neural evoked responses in the external carotid postganglionic sympathetic nerve of the cat using single and multiple shocks at pressor regions of the brain stem and spinal cord. Two distinct systems of vasopressor pathways were observed. One of these

was located in the periventricular gray and dorsolateral reticular formation of the medulla and had a latency of 70 to 140 ms, which is temporally consistent with the onset of the early EVR peaks. Although those investigators did not apply stimulation in synchrony with peak systole or diastole, they did examine the effects of raising blood pressure (norepinephrine administration). This had the effect of activating the baroreceptors for an extended period and either partially or completely blocked the averaged evoked nerve responses. In our method, baroreceptor activation corresponds to the systolic period of stimulation. Thus, the EVR may be generated through the same brain stem mechanisms described by those investigators.

If the EVR is a neurally mediated event, its presence in the brain requires participation of brain vascular nerves. This may be somewhat surprising because, even though the presence of autonomic nerves on cerebral arteries is well established (4, 5, 9, 11, 29), their function has remained obscure and controversial (33). Some authors have reported consistent responsiveness of cerebral arteries to electrical stimulation of such regions as the cervical sympathetic ganglion and the reticular formation (10, 11, 20, 22, 30). Such responses may not, however, result in marked cerebral blood flow changes (32). Thus, the role of sympathetic projections in regulating cerebral artery diameter in man remain uncertain. If it is demonstrated in future studies that the brain EVR is due to autonomic influences on brain vascular smooth muscle, the EVR could prove to be of value in the clinical assessment of the integrity of cerebral vasomotor pathways and cerebrovascular smooth muscle flexibility and may provide a new means for the experimental study of these nerves in human subjects.

The very short latency of the EVR tends to exclude local metabolic factors as contributing variables. Even if it were assumed that brief auditory tones induce very rapid metabolic changes in the brain and periphery, the accepted time course for such events to significantly influence the vasculature is still incongruent with the present data. In general, alteration of artery/vessel diameter by metabolic end products (i.e., autoregulation) such as carbon dioxide requires at least several seconds, as time is necessary for changes in metabolic demands to sufficiently alter their extracellular concentrations. Further, such an effect on metabolism (and the vasculature) would have to be occurring in a previously unreported on-off fashion as the adjacent no-stimulus trials (in which no EVRs were found) were randomly mixed with stimulus trials. This implies that the metabolic changes would themselves also have to terminate rapidly. Alternatively, the EVR may be a component of "anticipated" changes in metabolic demands. Although such preparatory responses have been reported in the periphery (24) it was only recently that primary cerebral vasodilation (i.e., in the absence of metabolic changes) was reported in the brain (31).

Conversely, the EVR may not have any significance in relation to metabolic processes but could simply be a component of the nervous system's obligatory reaction to brief auditory stimulation. In this regard, it is not clear from the present data whether the EVR is an expression of an OR. Sokolov (37) described the vascular OR as always consisting of vasoconstriction in the finger and vasodilation in the forehead, being the opposite for the DR. The shape of grand mean difference waves does not suggest a differential pattern of vasodilation or vasoconstriction in the finger and forehead photoplethysmograms. Further, cardiac cycle sensitivity has not been reported for ORs. Rather, they exhibit morphologically identical volumetric responses. Thus, the EVR doesn't seem to resemble the classic pattern of responses to a brief auditory stimulus.

The EVR is likely a result of afferent stimulation initiated by brain stem vasomotor centers. Involvement of higher brain centers such as cortex cannot be ruled out by the present data, but the fact that EVRs were elicited simply by task-independent (i.e., cognition-independent) stimulation, implies that participation of higher brain centers would not be required.

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