Noninvasive localization of brain-stem lesions in the cat with multimodality evoked potentials

Correlation with human head-injury data

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Multimodality evoked potential (MEP) data from over 300 comatose head-injured patients suggest that central nervous system dysfunction of the brain stem and/or hemispheres can be localized with this noninvasive neuroelectric technique. Based on this work, decerebrate motor posturing and prolonged coma are not associated with brain-stem dysfunction but rather with dysfunction of the hemispheres, while absent pupillary and oculocephalic responses are correlated with brain-stem dysfunction alone. However, the accuracy with which MEP data localized human brain-stem or hemispheric dysfunction could not be confirmed by pathological correlation because of low mortality and the small number of autopsies obtained in the patients who died. Therefore, this study was undertaken in an animal model of brain-stem lesion.

Complete brain-stem transections were made at the cervicomedullary junction, the medulla just caudal to the eighth nerve, and at the intercollicular region. All cortical visual evoked potential (VEP) peaks were reduced in amplitude and delayed by each of the brain-stem transections, but none of the peaks was abolished. In spite of brain-stem transection, VEP's can be used to gain information about hemispheric function. Somatosensory (SEP) and auditory cortically generated evoked potentials (AEP) were abolished by these brain-stem transections, but early-latency brain-stem SEP and AEP data could accurately localize specific areas of brain-stem dysfunction caused by the lesions. Observations made on human MEP data seem to be confirmed by these animal experiments. Correlations between human and cat MEP data are discussed.

Key Words: head injury • decerebrate posture • prolonged coma • multimodality evoked potentials • brain-stem lesion
Brain-stem localization with evoked potentials

vere head injury, using a method of assessing brain function other than the neurological examination, we studied over 300 comatose head-injured patients with multimodality evoked potentials (MEP), that is visual, somatosensory, and auditory cortical (VEP, SEP, AEP) and somatosensory and auditory early-latency, brain-stem evoked potentials. Our data suggested that in comatose head-injured patients, this noninvasive electrophysiological battery might be able to localize areas of dysfunction of the brain stem or hemispheres more reliably than the neurological examination. Correlations between loci of CNS dysfunction determined by MEP and the patient’s posttraumatic neurological condition suggested that decerebrate motor posturing and duration of coma were not associated with brain-stem dysfunction, whereas impaired oculocephalic and/or pupillary responses were reliable clinical indicators of brain-stem dysfunction. Decerebration and prolonged coma were consistently found in patients with MEP-defined hemispheric dysfunction, even when the brain stem was electrically normal.

The validity of hypotheses suggested by human head-injury MEP data, correlating clinical signs with areas of CNS dysfunction, depends on the accuracy with which MEP’s can localize dysfunctional brain. Peripheral stimulation of the somatosensory and auditory sensory systems has been shown to generate specific evoked potential wave peaks that arise from both brain-stem and cortical structures and can be recorded from the patient’s scalp. For cortical VEP wave peaks to be generated, subcortical elements of the visual system, such as optic nerves, chiasm, lateral geniculate bodies, must be integral. However, no specific VEP wave peaks recorded from scalp electrodes have yet been convincingly attributed to these subcortical structures. Our human data suggest that VEP’s can provide an index of hemispheric function perhaps independent of the brain stem. The VEP’s are only minimally altered in patients with severe brain-stem dysfunction caudal to the lateral geniculate bodies, but are dramatically changed by severe hemispheric dysfunction. Data of SEP’s and AEP’s also reflect hemispheric function, but brain-stem integrity is a necessary condition for this. In fact, the early latency or brain-stem evoked potentials of these two modalities not only indicate dysfunction of the brain stem but also appear able to localize the areas within the brain stem that are most compromised.

The localization of human CNS dysfunction based on MEP data could not be confirmed systematically by necropsy (only a small number of the 30% to 40% of severely head-injured patients who die have postmortem examinations). We therefore undertook the present study in an animal brain-stem lesion model to ascertain if VEP’s are altered by complete brain-stem transections caudal to the lateral geniculate bodies, and 2) to compare the accuracy with which somatosensory and auditory early-latency potentials localize lesioned areas within the brain stem.

**Materials and Methods**

**Animal Preparation**

Twenty-five conditioned cats, 10 control and 15 experimental, of either sex, weighing between 2.5 and 3.0 kg, were prepared in a similar manner. The animals were anesthetized intravenously with sodium methohexital (Brevital), 1 mg/kg. A cannula was placed in the femoral vein for drug administration, and in the femoral artery to monitor blood pressure and arterial blood gases. Tracheostomy was performed, and the animals were ventilated with a 4:1 concentration of N2O/O2. All surgical wounds were infiltrated with 1% xylocaine local anesthetic; this procedure was periodically repeated until the animals were sacrificed. Brevital was discontinued following the N2O/O2 ventilation and xylocaine tissue infiltration. A 0.2% solution of succinyllcholine chloride in normal saline was continuously infused via the femoral vein. Arterial blood gases were evaluated, respirator rate and volume adjusted, and sodium bicarbonate infused initially and again during the experiment so that the animals’ blood gases were maintained as follows: pO2 110 10 mm Hg; pCO2 30 4- 3 mm Hg; pH 7.40 4- 0.05; and bicarbonate 18 to 19 mEq/liter. To be included in this study, an animal had to have an initial hematocrit of between 30% and 40%, a mean arterial blood pressure that was initially and throughout the experiment between 120 and 140 mm Hg, and an initial rectal temperature of 39° 1 0.5°C that was subsequently maintained in this range by water-heated blankets. Arterial blood gas measurements were determined every 30 minutes, and temperature and mean arterial pressure were monitored continuously.

The animals were placed on a stereotaxic frame with hollow stainless steel ear bars. The scalp and muscles were reflected and holes drilled in the skull with a high-speed electric drill to accommodate the epidural electrodes and radiofrequency lesion rake (Figs. 1 and 2). Two epidural electrodes were placed in the skull on either side of midline at stereotaxic locations A4 and L-R16 for recording somatosensory and auditory early-latency evoked potentials, and two electrodes were placed at P3 and L-R4 to record VEP’s. A reference electrode was placed centrally in the bone of the nasal sinus and the animal grounded subcutaneously in the thigh. When the experiment was terminated, the cats were given a lethal dose of sodium pentobarbital. Their brains were removed and processed for routine light microscopy after transcardial perfusion with 10% buffered neutral formalin. The sections were stained with hematoxylin and eosin.

**Multimodality Evoked Potentials**

Multimodality evoked potentials, somatosensory and auditory brain-stem or early-latency potentials

J. Neurosurg. / Volume 54 / June, 1981 741
FIG. 1. Animal model utilizing visual (strobe light), auditory (sound click), and somatosensory (median nerve shock) evoked potentials to identify the location and extent of brain-stem dysfunction following radiofrequency brain-stem lesions. Inset: Placement of the electroencephalographic leads. A: Reference electrode for evoked potential. B: Recording electrodes for evoked potential. C: Drill holes for poles of lesion rake.

FIG. 2. Radiofrequency lesion rake designed to produce a complete brain-stem transection, 2 to 3 mm thick. The height, dorsoventral diameter of the brain stem, and width of the lesion are adjustable by varying the length of the uninsulated poles and the distance between the poles, respectively.

(neuroelectric potentials generated within 10 msec of stimulation), as well as longer-latency visual, auditory, and somatosensory cortical evoked potentials, were obtained from each animal. Evoked electrical activity was recorded from epidural electrodes, amplified 5000 times (total system gain includes pre-amplifier, amplifier, and computer gain), and filtered through a bandpass of 30 Hz to 3 KHz for brain-stem potentials or 3 Hz to 1 KHz for cortical evoked potentials. Two channels of evoked electrical activity were simultaneously averaged by a computer with a 1024 address, 12 bit/address memory. A sampling rate of 50 KHz (20 μsec bin width) and 10.2 KHz (90 μsec bin width) was used for brain-stem and cortical evoked potentials, respectively. The analysis epoch for brain-stem potentials was 40 msec, while that for cortical evoked potentials was 100 msec. The evoked potentials were averaged on-line, viewed on an oscilloscope, and stored on IBM-compatible digital tape for off-line analysis. An x-y plotter was available for immediate hard-copy storage of data.

Somatosensory Evoked Potentials. Both brain-stem and cortical/SEP’s were recorded simultaneously from an ipsilateral and contralateral epidural electrode placed over the primary sensory receiving area (A, L-R, referenced to the centronasal bone electrode. The left then the right median nerve was stimulated by two No. 25 needles placed proximal to the animal’s paw over the median nerve (Fig. 1). Generally, a 0.2 msec duration, 4-volt pulse delivered through a stimulation isolation box at a rate of 1 pulse per second (PPS) for the cortical and 5 PPS for the brain-stem responses gave a maximal amplitude SEP. One hundred twenty-eight stimulus trials were averaged to obtain somatosensory cortical
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FIG. 3. Radiofrequency lesion of the brain stem has a "postage stamp" shape (2 to 3 mm thick) and was produced by the lesion rake with minimal damage to nontarget brain parenchyma. The lesion shown (bottom left) was produced in the intercollicular region of cat brain stem by the passage of four electrode poles dorsoventrally through the overlying hemispheres.

Evoked responses, and 512 were averaged for somatosensory brain-stem evoked responses. Each set of averages was repeated three times to assure consistency within an animal's response.

Auditory Evoked Potentials. Both brain-stem and cortical AEP's were recorded simultaneously from an ipsilateral and contralateral epidural electrode (A, L-R10) referenced to the centronasal bone electrode. The left then the right ear was stimulated with an 80-db tone pip having a duration of 0.2 msec at a rate of 1 PPS for cortical and 5 PPS for brain-stem responses. One hundred twenty-eight trials were averaged for the auditory cortical evoked responses, and 512 for auditory brain-stem evoked responses. Each set of averages was repeated three times to assure consistency. The stereotaxic ear bars have a central lumen for the delivery of sound to the tympanic membrane. A small microphone was attached to the ear bars via hard rubber tubing (Fig. 1). The delay caused by this tubing length and the length of the ear bar is 1.6 msec and is subtracted in calculating wave latencies.

Visual Evoked Potentials. Visual evoked potentials were recorded from two symmetrically placed electrodes just in front of the bony tentorium over the occipital lobes (P, L-R6) referenced to the centronasal bone electrode. The left then the right eye was stimulated after a mydriatic agent was used to maximally dilate the pupils. A photo stimulator was positioned 10 inches from the cat's nasion, its intensity set to deliver a maximal amplitude VEP (Fig. 1). One hundred twenty-eight trials were averaged and repeated three times for consistency. The stimulation repetition rate was 1 PPS and its duration 10 μsec.

Electroencephalography

Each animal's electroencephalogram (EEG) was continuously recorded from the epidural electrodes referenced to the central nasal electrode via amplifiers with a filter bandpass of 0.5 to 50 Hz. The EEG hard copy was provided by a dynagraph recorder adjusted so that a 50-μV calibration pulse caused a 10-mm pen deflection.

Brain-Stem Transection

Complete brain-stem transections were accomplished in experimental animals by radiofrequency lesions (300 mA for 10 sec) delivered through a four-pronged lesion rake (Fig. 2). The lesion rake was designed to completely transect a 2- to 3-mm thick section of brain stem (Fig. 3). The width of the postage stamp-shaped brain-stem lesion produced when radiofrequency current was applied to the rake was controlled by the distance between each of the four poles. The height of the lesion or its dorsoventral diameter was determined by adjusting the uninsulated length of each pole: the rest of the pole was insulated with Tef-
FIG. 4. Approximate location of radiofrequency brain-stem transections in the cat: intercollicular; medullary, just caudal to the eighth nerve entrance in the brain stem; and at the cervicomedullary junction.

Three control and five experimental animals it was introduced at the cervicomedullary junction (CM) (Fig. 4). Radiofrequency lesions were made only in the brain stem of the 15 experimental animals.

In all animals, MEP's were recorded at least three times during each time period: 1) prior to rake insertion; 2) between 5 and 20 minutes following rake insertion or lesion production, depending on the animal; and 3) hourly for 6 hours. The animal's temperature, arterial blood gases, and mean arterial pressure were carefully maintained within the ranges described above. Each animal's EEG was continuously recorded to monitor cortical electrical activity. All animals were sacrificed and their brains perfused and studied in a similar manner.

Data Analysis

Twenty-five animals were selected for analysis from a total of 42. The remaining 17 cats were eliminated from this study (but used for other experiments) because of one or more of the following reasons: 1) the physiological criteria established for this study were not satisfied; 2) the data obtained were not complete; 3) a greater than 10% change in amplitude of one or more selected evoked potential waves occurred prior to rake insertion; and 4) histological study of the specimens indicated incorrect rake placement or incomplete brain-stem transection.

Evoked potential wave latencies were measured from time of stimulation to wave peak in milliseconds; wave amplitudes were measured peak to following trough in microvolts. In the figures, an upward deflection of an evoked potential peak represents averaged electrical activity recorded from an epidural electrode that was positive relative to the electrical activity of the reference electrode (Figs. 5, 6, and 7). Peaks were identified in this report for a given modality by the order of occurrence of their latencies, and this value was prefixed by either a P (positive) or N (negative) to indicate the relative polarity of the peak. For example, the first peak selected for analysis in the brain-stem AEP was positive and occurred at about 1.1 msec from time of stimulation; it was identified by P1. The second through sixth brain-stem AEP peaks selected were also positive and identified as P2, P3, P4, P5, and P6, respectively. Following the sixth peak, a negative peak was analyzed and identified as N1, and so on (Table 3). A full description of the analyzed

<table>
<thead>
<tr>
<th>Feature</th>
<th>P1 (msec)</th>
<th>N1 (msec)</th>
<th>P2 (msec)</th>
<th>N2 (msec)</th>
<th>P3 (msec)</th>
<th>N3 (msec)</th>
<th>P4 (msec)</th>
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<tr>
<td>latency</td>
<td>14.20</td>
<td>17.50</td>
<td>21.30</td>
<td>25.40</td>
<td>37.30</td>
<td>52.60</td>
<td>72.50</td>
</tr>
<tr>
<td>(msec)</td>
<td>± 0.84</td>
<td>± 0.69</td>
<td>± 0.92</td>
<td>± 0.87</td>
<td>± 2.11</td>
<td>± 2.83</td>
<td>± 2.96</td>
</tr>
<tr>
<td>amplitude</td>
<td>19.10</td>
<td>5.40</td>
<td>10.50</td>
<td>8.30</td>
<td>12.50</td>
<td>10.60</td>
<td>11.80</td>
</tr>
<tr>
<td>(µV)</td>
<td>± 1.07</td>
<td>± 1.39</td>
<td>± 1.09</td>
<td>± 1.12</td>
<td>± 0.98</td>
<td>± 0.91</td>
<td>± 0.79</td>
</tr>
</tbody>
</table>

*Mean and standard deviation. For a description of peaks see text.
Brain-stem localization with evoked potentials

TABLE 2
Somatosensory evoked potentials: mean latency and amplitude of selected peaks*

<table>
<thead>
<tr>
<th>Feature</th>
<th>Brain-Stem Potentials</th>
<th>Cortical Potentials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P1</td>
<td>P2</td>
</tr>
<tr>
<td>latency (msec)</td>
<td>3.97</td>
<td>5.22</td>
</tr>
<tr>
<td>amplitude (μV)</td>
<td>± 0.25</td>
<td>± 0.27</td>
</tr>
</tbody>
</table>

*Mean and standard deviation. For a description of peaks see text.

The wave peaks of the brain-stem AEP were P1, P2, P3, P4, P5, P6, N1, P7, N2, and P8. For each modality, peak latency and amplitude values utilized in the statistical analyses represented the mean of three measurements derived from three different averaged evoked potentials obtained during a designated time period (Table 3).

Peak data stored on digital tapes were analyzed off-line by a computer-assisted interactive program that identified wave peaks, calculated mean latencies and amplitudes, and organized these wave measurements into tabular form for statistical analysis.

Amplitudes and latencies were measured for 7, 8, and 10 selected peaks for the visual, somatosensory, and auditory modalities, respectively (Tables 1, 2, and 3). Three experiments were performed, marked by the three locations of the rake. Evoked potential measurements used in the statistical analysis were selected from three time points: 1) a baseline measurement; 2) 5 to 20 minutes after rake insertion for controls or post-lesion production for experimental animals; and 3) 6 hours after rake insertion. Any peak not identifiable following a lesion was regarded as missing. Clearly, when a peak present in all controls could not be identified in all experimental animals, an important and significant (p < 0.05) treatment effect existed. The latency and amplitude of each remaining peak was subjected to a multivariate analysis of variance where the three time points correspond to split-plots in a completely randomized two-treatment design. A significant treatment by time interaction indicated changes in the peak's structure (either latency or amplitude or both) that differed for the control and treatment groups and, thus, was considered a lesion effect. Significant univariate analyses were reviewed to determine if the difference in peak structure was primarily located in either latency or amplitude shifts. Duration and magnitude of the treatment effect was examined via plots of mean response.

Results

Visual Evoked Potentials

Seven consistently identifiable VEP peaks that occurred in the first 100 msec following stimulation were analyzed in the control and experimental animals designated P1, N1, P2, N2, P3, N3, and P4 (Fig. 5, Table 1). In the 10 control animals, no significant change from baseline values of either peak latency or amplitude occurred in the seven analyzed VEP peaks regardless of rake location (cervicomedullary junction, medullary, or intercollicular) at a time period 5 to 20 minutes following rake insertion or 6 hours later. Insertion of the lesion rake was not sufficient to produce changes in the animals' visual evoked potential.

While none of the peaks disappeared, a significant treatment by time effect indicating an alteration of the VEP waveform was present in all the experimental animals for both time periods: 5 to 20 minutes and 6 hours (post-lesion). The amplitude was reduced and the latency increased for five peaks (P1, P2, N2, N3, P4) when cervicomedullary junction lesions were made (Fig. 5), for five peaks (P1, N1, P2, P3, N3) when medullary lesions were made, and for three peaks (N1, P3, N3) when intercollicular lesions were produced (Table 4). Those peaks not significantly changed from

TABLE 3
Auditory evoked potentials: mean latency and amplitude of selected peaks*

<table>
<thead>
<tr>
<th>Feature</th>
<th>Brain-Stem Potentials</th>
<th>Cortical Potentials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P1</td>
<td>P2</td>
</tr>
<tr>
<td>latency (msec)</td>
<td>1.48</td>
<td>2.56</td>
</tr>
<tr>
<td>amplitude (μV)</td>
<td>± 0.34</td>
<td>± 0.25</td>
</tr>
</tbody>
</table>

*Mean and standard deviation. For a description of peaks see text.
R. P. Greenberg, D. M. Stablein and D. P. Becker

**TABLE 4**

Visual evoked potentials: effects of brain-stem lesions*

<table>
<thead>
<tr>
<th>Location of Lesion</th>
<th>P1</th>
<th>N1</th>
<th>P2</th>
<th>N2</th>
<th>P3</th>
<th>N3</th>
<th>P4</th>
</tr>
</thead>
<tbody>
<tr>
<td>intercollicular</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>medullary</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>NS</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>cervico-medullary</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*A significant treatment by time interaction indicates a change of peak latency and amplitude in lesioned animals compared to controls. NS indicates that the peak was not significantly changed by the lesion. For a description of peaks see text.

**TABLE 5**

Visual evoked potential peak latency and amplitude changes*

<table>
<thead>
<tr>
<th>Feature</th>
<th>P1</th>
<th>N1</th>
<th>P2</th>
<th>N2</th>
<th>P3</th>
<th>N3</th>
<th>P4</th>
</tr>
</thead>
<tbody>
<tr>
<td>latency increase</td>
<td>17.3</td>
<td>11.4</td>
<td>13.5</td>
<td>13.1</td>
<td>12.1</td>
<td>14</td>
<td>13.2</td>
</tr>
<tr>
<td>amplitude decay</td>
<td>50</td>
<td>14</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>42</td>
<td>45</td>
</tr>
</tbody>
</table>

*Peak latency increase and amplitude decay are expressed as percent change from baseline. For a description of peaks see text.

Fig. 5. Visual evoked potentials before (upper) and after (lower) production of a lesion at the cervicomedullary junction. While no visual evoked potential wave peak was abolished by any of the brain-stem lesions, peak amplitude decreased and peak latency increased immediately following each lesion. These changes were still present 6 hours later.

Baseline as a result of one of the three lesion locations were nevertheless altered. Their amplitudes were reduced and latencies increased. These VEP changes for all 15 experimental animals are expressed as mean percent change from baseline peak amplitudes and

latencies in Table 5. These data suggest that the three lesions produce similar alterations of the VEP waveform and that these alterations cannot be utilized to reliably identify the location of a specific brain-stem lesion.

**Somatosensory Evoked Potentials**

Eight SEP wave peaks were analyzed in the control and experimental animals. The first five are considered to be SEP brain-stem waves (P1, P2, P3, P4, P5); these were followed by three SEP cortical waves (N1, P6, N2) (Fig. 6, Table 2). Insertion of the lesion rake caused no significant SEP waveform alteration of either the brain-stem or cortical potentials, 5 to 20 minutes or 6 hours later.

Three significant, different treatment effects were produced by each of the brain-stem lesions. In all but one case, peak change was indicated by the abolition of the peak as a result of the lesion. Following brain-stem transection at the cervicomedullary junction, only the P1 wave peak remained at the two post-lesion periods analyzed. This peak was unchanged from baseline (Table 6). Thus, P1 must be generated in structures caudal to the cervicomedullary junction and the nuclei of the dorsal columns. When the brain stem was transected just caudal to the nuclei of the eighth nerve but rostral to the nuclei of the dorsal column (Lesion M), two SEP brain-stem peaks remained (P1 and P2), while all the remaining waves were abolished.

Fig. 6. Somatosensory evoked potential before (upper) and after (lower) complete brain-stem transection of the medulla just caudal to the entrance of the eighth nerve. The P1 peak represents activity generated caudal to the cervicomedullary junction and was unchanged by this lesion. The P2 peak, although still identifiable, was significantly altered, both in amplitude (decreased) and latency (increased), by the lesion. Note change in amplification, y-axis in lower tracing.
Brain-stem localization with evoked potentials

### TABLE 6
**Somatosensory evoked potentials: effects of brain-stem lesions***

<table>
<thead>
<tr>
<th>Location of Lesion</th>
<th>P₁</th>
<th>P₂</th>
<th>P₃</th>
<th>P₄</th>
<th>P₅</th>
<th>N₁</th>
<th>P₆</th>
<th>N₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>intercollicular</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
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<tr>
<td>medullary</td>
<td>NS</td>
<td>&lt;0.01</td>
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<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>cervico-medullary junction</td>
<td>NS</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

* -- = absence of peak for 6 hours following lesions.

Significant treatment by time interaction indicates a change of peak latency and amplitude in lesioned animals compared to control. NS indicates that the peak was not significantly changed by the lesion. For a description of peaks see text.

for both post-lesion time periods (Fig. 6). However, P₂ was significantly altered in both latency and amplitude (Table 6). Thus, P₂ would appear to be generated from somatosensory system structures in the medulla oblongata, that is, nuclei of the dorsal columns and/or medial lemnisci. As a result of intercollicular brain-stem transection, all SEP peaks were abolished except P₁, P₃, and P₄ for both post-lesion time periods (Table 6). Therefore, P₄ must be generated from structures located between the medullary lesion just caudal to the entrance of the eighth nerve and the intercollicular region, and may receive a contribution from cerebellar generators.

**Auditory Evoked Potentials**

Ten AEP wave peaks were analyzed in the control and experimental animals. The first six waves, P₁, P₂, P₃, P₄, P₅, and P₆, are thought to be generated in brain-stem structures, while the remaining four waves, N₁, P₇, N₂, and P₈, are thought to be cortical in origin (Fig. 7, Table 3).¹⁻⁴,¹₀,¹₁,²¹,²₄,²₆,²₉ No significant alteration of these peaks occurred following rake insertion at any of the three rake locations or time periods analyzed.

There were no significant AEP wave peak alterations following brain-stem transection at the cervico-medullary junction and medulla just caudal to the eighth nerve nuclei. When the brain stem was transected between the superior and inferior colliculi, wave peaks N₁, P₇, N₂, and P₈ were abolished while wave peaks P₁, P₂, P₃, P₄, P₅, and P₆ remained unchanged (Table 7). The negative peak N₁ may be the first wave generated in the cat cortex. Furthermore, with the abolition of the N₁, P₇, N₂ complex, a series of alternating positive and negative waves appeared following intercollicular lesions at latencies 8 to 10 through 20 to 30 msec (bottom waveform). Fig. 7. Auditory evoked potentials before (upper) and after (lower) complete brain-stem transection at the intercollicular region. The first six positive peaks were unchanged from baseline, but all subsequent selected peaks, N₁, P₇, N₂, were abolished. A series of alternating positive and negative waves appeared following intercollicular lesions at latencies 8 to 10 through 20 to 30 msec (bottom waveform).

### TABLE 7
**Auditory evoked potentials: effects of brain-stem lesions***

<table>
<thead>
<tr>
<th>Location of Lesion</th>
<th>P₁</th>
<th>P₂</th>
<th>P₃</th>
<th>P₄</th>
<th>P₅</th>
<th>N₁</th>
<th>P₇</th>
<th>N₂</th>
<th>P₈</th>
</tr>
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<tbody>
<tr>
<td>intercollicular</td>
<td>NS</td>
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<td>NS</td>
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<td>NS</td>
<td>NS</td>
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* -- = abolished peak replaced by periodic alternating positive-negative waves, see text. NS indicates that the peak was not significantly changed by the lesion. For a description of peaks see text.

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from 2 to 10 Hz, the period of the alternating waves remained constant. In two animals that did not have their data analyzed for this study because the rake and subsequently the brain-stem lesion was incorrectly located just caudal to the inferior colliculi, the alternating waves were nonetheless detected following the transection. They appear to be generated in the pontomedullary region rostral to the entrance of the eighth nerve in the brain stem.

**Discussion**

**Visual Evoked Potentials**

While VEP wave peak amplitudes were decreased and latencies increased by complete brain-stem transections at the intercollicular, medullary, or cervico-medullary junctions, no peak was abolished. These VEP data in cats suggest that not only do brain-stem structures caudal to the lateral geniculate bodies influence the cortical VEP, but CNS structures caudal to the cervico-medullary junction have this effect as well. However, VEP wave morphology is not sufficiently altered by brain-stem lesions to obviate their utility as indicants of hemispheric function. (We did not study in this experiment the specific hemispheric regions that respond to visual stimuli and take part in the generation of the cortical VEP). In three animals following brain-stem transection, hypotension inadvertently occurred and was corrected (data from these animals were excluded from analysis). Cortical VEP wave peaks, although altered by the transection, nevertheless, reflected the fall and subsequent return to normal of the blood pressure in our brain-stem transected cats in a similar manner to VEP’s in cats without brain-stem lesions that were subjected to a similar hypotensive maneuver.

In order to evaluate human CNS dysfunction following head injury with evoked potentials, it is important to study patients with VEP’s, as this modality is an index of hemispheric function even after brain-stem lesions. Severe alterations or absence of somatosensory and auditory cortical evoked potential wave peaks cannot confidently be interpreted to mean hemispheric dysfunction, because both these evoked potential modalities depend upon the integrity of brain-stem as well as hemispheric structures. Data from VEP wave peaks supplement SEP and AEP findings in evaluating cortical function when the brain stem is intact, but VEP wave peaks are the only evoked potential indicant of hemispheric function in the presence of a severe brain-stem lesion. This finding is suggested by the animal data as well as the results of our work with MEP’s in head-injured patients.

**Somatosensory Evoked Potentials**

Cortical SEP activity represented by wave peaks P1, N1, P2, and N2 was uniformly abolished by the three brain-stem transections. Distinctly different waveform alterations of the early-latency brain-stem potentials resulted from brain-stem transection at each of the chosen locations (cervico-medullary junction, medullary, and intercollicular). Cervico-medullary transections that obliterated the nuclei of the dorsal columns abolished all wave peaks except P1. It would appear that this potential is generated by the advancing depolarization in the spinal cord generated by median nerve shock pulses. This finding is in agreement with the work of Iragui-Madoz and Wiederholt, who suggest a cervical posterior column source for this wave. Medullary transections just caudal to the eighth nerve nuclei abolished all peaks except P1 and P2. Our data suggest that P2 is generated in the nuclei of the dorsal columns, the medullary medial lemnisci, or a combination of both. Although still present following the medullary transections, P2 was significantly altered, both with respect to amplitude (decreased) and latency (increased) (p < 0.01). Intercollicular transections produce SEP waveforms that contain only P1, P2, and P3. The P3 wave may be generated by nuclei in the cerebellum or structures pertaining to cerebellar tracts, such as those of the inferior cerebellar peduncle. Cerebellar anatomy was well preserved after rake insertion and lesion production. Furthermore, SEP’s did not show change in control animals when the poles of the lesion rake were passed through the cerebellum for positioning in the brain stem prior to lesion production. Thus, cerebellar as well as medial lemniscal contributions could provide generator sources for P3. A peak not considered cortical in origin, P4, was abolished by all three brain-stem lesions. It could originate in the thalamus or thalamocortical radiation.

In man, we record, as do others, three or four positive somatosensory early-latency potentials (< 14- to 15-msec latencies) prior to the first cortically generated negative peak (at 20 msec in adults), that is, P1, P2, P3, P4, and N4. Based on our limited autopsy material, we believe that in man P1 and P2 are generated in the medulla from the nuclei of the dorsal columns, the medial lemnisci, or cerebellar structures. Our patients with high, complete traumatic cervical cord transections do not have the early-latency peak P3 nor any wave in the somatosensory system that would typically follow P3. The P1 and P2 waves remain intact following high cervical-cord lesions. Furthermore, P1, P2, P3, and P4 can be recorded in patients with rostrocaudal brain-stem deterioration that spares only medullary function. Therefore, we believe that human P1 and P2 are comparable to the cat P1 and P2, as these wave peaks are probably generated in the nuclei of the dorsal columns, and other medullary and possibly cerebellar structures. These data suggest that in man somatosensory early-latency data are useful in localizing brain-stem lesions in general. Moreover, they may be able to identify the specific lesion location within the brain stem if structures caudal to the level where the eighth nerve enters the brain stem are involved.

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Auditory Evoked Potentials

Auditory cortical evoked potential activity was abolished only by the intercollicular brain-stem transections. Cervicomedullary and medullary (just caudal to eighth nerve nuclei) transections did not significantly alter the auditory evoked potential wave peaks.

Following intercollicular lesions, waves N1, P1, N2, and P2 were abolished, whereas wave peaks P1, P2, P3, P4, P5, and P6 were not significantly altered from baseline values. The first six waves are clearly generated in a structure or structures caudal to the intercollicular region. Furthermore, in two additional cats in which rake location inadvertently transected the brain stem caudal to the inferior colliculi (data from these cats were not used for analysis), P1 through P5 remained unchanged, suggesting that the inferior colliculi play an insignificant role in early-latency AEP peak generation. A series of alternating positive, negative waves were clearly identifiable following all intercollicular lesions. These waves do not appear to be similar to the frequency following response, as they maintained a constant period in spite of frequency variations of the auditory stimulus pulse. They occurred and appeared unchanged at stimulus rates of between 2 and 10 Hz with equal amplitudes and latencies. These data suggest that the generators of brain-stem AEP's P1, P2, P3, P4, and P5 in the cat may be in the orderly sequence of structures previously described, namely, eighth nerve action potential, cochlear nuclei, superior olivary complex, lateral lemnisci, and inferior colliculi. Instead, it is possible that the ventral cochlear nuclei, trapezoid body, and possibly superior olivary complex, individually or in combination, could be generating trains of waveforms as a result of auditory stimuli. The alternating waveforms can be recognized with difficulty in control cats where they appear as indistinct waveforms that follow P4 or P5. The latter two peaks are described by most workers, and appear to be rather constant findings, whereas positive wave peaks between 6 and 10 msec are generally not quantified because they are inconsistently present. Elimination by intercollicular brain-stem transection of wave N1, as well as the cortical waves that follow allows the alternating wave peaks to be readily identified. The sinusoidal pattern can often be traced up to 20 to 30 msec after stimulation.

Our MEP data obtained from patients with brain-stem dysfunction as a result of severe head injury typically reveal severe alterations of the brain-stem AEP's. Distinct wave peaks following P1 (eighth nerve action potential) are not present in these patients. Instead, only one delayed amorphous positive peak at about 6 msec can be identified. Alternating positive, negative wave peaks following P4 are often recognizable. In the brain-stem AEP's of these patients, the N1 wave is either absent or manifested by a low-amplitude delayed-latency peak. Auditory cortical wave peaks are abolished. In the animal model, lesions of the midbrain at or just caudal to the inferior colliculi produce a brain-stem AEP pattern that most closely approximates the same pattern seen in human brain-stem dysfunction following severe head injury. In our patients, correlations between this brain-stem AEP pattern and autopsy findings suggest its association with midbrain lesions.

We believe that our human MEP data and the results of this animal experiment lend strong electrophysiological support to those workers who believe, based on clinical and pathological findings, that human decerebrate posture is not an invariable sign of brain-stem dysfunction. Furthermore, the presence of prolonged coma can often result from hemispheric dysfunction and as such may not be as grave a prognostic sign as more definite clinical evidence of brain-stem compromise, such as absent pupillary or oculocephalic responses.

References


This work was supported in part by NINCDS Grant NS-12587, and Teacher-Investigator Award K07-NS 346-03 to Dr. Greenberg. This work was submitted by Dr. Greenberg in partial fulfillment of requirements for the Ph.D. degree, Department of Physiology, Virginia Commonwealth University, Richmond, Virginia.

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