Comparison of the Somatosensory Evoked Potential and the Direct Cortical Response Following Severe Incomplete Global Ischemia: Selective Vulnerability of the White Matter Conduction Pathways

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SUMMARY Eight cats were subjected to graded hemorrhagic hypotension following bilateral carotid ligation to produce incomplete global cerebral ischemia. Three additional cats served as controls. The somatosensory evoked potential (SEP) and direct cortical response (DCR) were monitored in all animals and in each case, the cortical component of the SEP was abolished during progressive ischemia while the morphology of the DCR was well-preserved but with reduced amplitude. Determinations of adenosine triphosphate (ATP), phosphocreatine (PCr), and lactate levels in cerebral cortex and white matter were made in five experimental cats and the three controls. At the time of failure of the cortical SEP, PCr was dramatically reduced and lactate moderately elevated in the white matter while ATP remained unchanged. Cortical lactate was only mildly elevated and PCr and ATP were unchanged accounting for preservation of the DCR. In this model of global ischemia, abolition of the cortical SEP is due to a block of stimulus conduction in white matter projection pathways. A hypothesis to explain the observed metabolic changes is presented and correlation is made to clinical situations.

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AS NEURONAL FUNCTION is affected by developing ischemia, cerebral electrical activity is necessarily altered. The ease with which this electrical activity can be monitored in the clinical setting on a continuous basis in comparison to measures of cerebral blood flow has prompted many investigators to study the electroencephalogram (EEG), the somatosensory evoked potential (SEP) and the direct cortical response (DCR) as potential indices of cerebral flow. The large, negative wave of the DCR is a post-synaptic potential generated by apical dendrites excited by axons in the molecular layer of the cortex. It is not attenuated by isolation from underlying subcortical structures, and therefore specifically reflects cortical function. The amplitude of the DCR has been found to be progressively attenuated with advancing ischemia. The SEP may reflect blood flow alterations at any point along the sensory pathway manifested by reduction in the amplitude of the primary cortical wave and by a lengthening of the conduction time of the stimulus to the cortex. The EEG is a widespread intraoperative monitor of cerebral ischemia during carotid endarterectomy but is the least specific. It has been suggested that the SEP may more accurately reflect the adequacy of cerebral flow.

In a model of global ischemia in the cat, we have previously demonstrated that failure of the cortical wave of the SEP can occur with a block of stimulus conduction through the white matter. This occurs in the cat when blood flow in white matter falls below 14 ml/100 gm/min and white matter ATP is below 40% of control stores. Cortical ATP, however, remained at 84% of control reflecting continued perfusion of cortex and we hypothesized that cortical energy metabolism would be adequate to generate a response should a stimulus volley be able to penetrate the white matter projections. This has important implications when interpreting the cause of failure of the cortical wave of the SEP in conditions of global ischemia.

This study was undertaken in the cat subjected to graded hemorrhagic hypotension following carotid ligation to produce incomplete global ischemia. The purpose of this study is to assess the functional state of the cortex at the point of failure of the cortical SEP by comparing the corresponding changes in the DCR.

Materials and Methods

Eleven adult cats, each weighing 3.4 to 4.7 kg, were premedicated with atropine 0.03 mg/kg and ketamine 25–35 mg/kg IM. Intravenous and femoral arterial catheters were placed and blood pressure was continuously monitored along with intermittent analysis of arterial blood gases. Body temperature was measured with a rectal probe and kept near 37° C with a warming pad. Platinum needle electrodes were placed on the median nerve of the foreleg and stimuli were given as 0.1 msec duration square waves at four per second with voltage adjusted to twice threshold levels for paw twitch (10 to 12 volts) to generate the SEP. The recording system was adjusted to a bandwidth of 3 to 3000 Hz and averaging performed over 256 responses. Endotracheal intubation was then performed and nitrous oxide and oxygen 3:1 administered as an anesthetic agent via controlled ventilation following muscular paralysis with pancuronium bromide 0.05 mg/kg as needed. Respirations were regulated to maintain a PaCO₂ of

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placed rigidly in a stereotaxic frame. Screw electrodes were placed in the skull on the right side contralateral to the stimulating paw electrodes, 1 cm lateral to the midline on the coronal suture and in the midline over the frontal sinus for recording the EEG. A 2 × 3 cm craniectomy was made on the left and the dura opened widely. A silastic leaflet with embedded 1 mm platinum disc electrodes (Progress Mankind Technology) was placed over the anterior suprasylvian gyrus. This leaflet is constructed such that two stimulating electrodes are placed 1 mm apart and a recording electrode placed 6 mm distant on the isoelectric line. Two platinum needle electrodes were placed in the ipsilateral temporals muscle to serve as reference and ground. To record the DCR, stimuli were given as 1–2 mAmp square wave pulses of 0.1 msec duration. The DCR signal was recorded with a differential amplifier having a common mode rejection ratio of 100,000:1 and set to a bandwidth of 1 to 3000 Hz. The DCR was averaged over 10 stimuli given 1 per second to eliminate baseline drift. Typical SEP and DCR waveforms are demonstrated in figure 1.

After obtaining a satisfactory set of baseline signals, the carotid arteries were ligated in eight cats and blood was withdrawn from the femoral artery catheter via a Harvard pump at a rate of 1 cc/min. The SEP and DCR were monitored at frequent intervals until the cortical SEP could not be obtained. This required approximately 2 hours and a mean blood pressure of approximately 60 torr. In five of these animals, the brains were quick frozen in situ with liquid nitrogen and removed for biochemical determination of cortical and white matter adenosine triphosphate (ATP), phosphocreatine (PCr) and lactate (Lac) levels. From each brain, two cortical and two white matter samples were taken from both the right and left hemispheres at the suprasylvian gyrus. The samples were dissected at −25° C, weighed (0.5 to 1.5 mg), and extracted with 0.1 N NaOH in methanol. The extracts were heated at 60° C and then assayed by enzymatic fluorometric methods. Three animals did not undergo carotid ligation nor graded hemorrhage but were prepped in the identical fashion and the DCR and SEP recorded over a period of two hours. The brains were then frozen to serve as controls. The result of each pair of brain samples was averaged. The five experimental and three control brains were then considered as separate groups to evaluate the possibility of right-left inter-hemispheric differences in ATP, PCr and lactate and the data evaluated using the paired t-test. As will be discussed, no significant right-left differences were observed. The right and left values were then averaged for each brain and the group of five experimental brains compared to the group of three control brains using the unpaired t-test.

Results

The typical control somatosensory evoked potential and direct cortical response is shown in figure 1. The large primary cortical wave of the SEP (V) following the far-field potentials was easily seen in all animals. Control latency measured 12.7 ± 0.4 msec and is consistent with our previously published results. Control DCR peak to peak amplitude measured 200–500 microvolts and the peak occurred 10.5 ± 1.08 msec following the stimulus. This is also similar to previously published values in cat cortex.

Following carotid ligation in eight animals, blood was slowly withdrawn while the SER and DCR were periodically recorded. In all animals, latency and amplitude changes occurred first in the SER in the manner which we have previously described. A delay in conduction of the stimulus from the thalamus to the cortex was followed by amplitude changes in the primary cortical wave. The cortical wave of the SER was abolished in all cats with a mean systemic blood pressure of 50–60 torr. EEG revealed slow wave forms in 5 cats and burst-suppression in the three others. During the period when the cortical wave of the SEP was abolished, the DCR morphology remained well-preserved (fig. 1) with an amplitude 50–90% of control (mean 70% ± 15%). No consistent change in DCR latency was observed.

ATP, phosphocreatine, and lactate levels were determined in the cortex and white matter of five experimental animals and the three controls (table 1). Since the SER and DCR were measured from opposite hemispheres, and to determine the possible effect of the craniectomy, dural opening and patch contact on the left hemisphere, right-left comparisons of energy metabolites were made in the experimental and control groups. No significant differences were seen although a trend toward higher cortical lactate (p ≤ .10) on the side of the craniectomy was identified in both groups. A trend toward lower ATP and PCr and higher lactate (p ≤ .10) was seen in the white matter on the side of the craniectomy in the experimental group. At the time of failure of the cortical wave of the SEP in the experimental cats, significant elevations in cortical lactate were observed compared to the control cats (p ≤ .001) but there were no changes in cortical ATP or PCr (fig. 1).
White matter ATP was also unchanged but a significant reduction was seen in white matter PCr ($p \leq .001$) as well as a moderate elevation in white matter lactate ($p \leq .001$) (fig. 2).

**Discussion**

Many investigators have related changes in the SEP cortical wave to alterations in cortical flow and metabolism. Our previous work in this model of global ischemia in the cat suggested that failure in generation of the cortical wave of the SEP can occur when a severe depletion of energy substrates occurs in the white matter projections resulting in a block of stimulus conduction. We proposed that cortical energy levels remained adequate to generate a response should a stimulus volley be able to penetrate the white matter conduction pathways. Generation of the DCR depends exclusively on cortical function and was used in the present experiment to test this hypothesis. At the point of abolition of the cortical wave of the SEP, the DCR was only mildly altered indicating that the failure of the SEP is in response to conduction pathway ischemia.

Consistent moderate reductions in cortical blood flow occur with mean blood pressures of 50–60 torr in the face of bilateral carotid occlusion in the cat. Although blood flow was not measured in the present experiments because of technical limitations, we observed reductions in the DCR amplitude coincident with the expected reduction in cortical flow. Other investigators have demonstrated a graded reduction of the DCR amplitude with a reduction in the cortical blood flow. Statistically significant right-left differences in energy metabolites were not observed in this model of global ischemia. However, a trend toward elevated lactate and reduced ATP and PCr was seen on the side of the craniectomy and electrode patch. Since the DCR was measured from this hemisphere and the SEP from the unexpected hemisphere, the experimental model can be considered a worst-case for the DCR compared to the SEP.

The present experiment failed to show significant differences between control and experimental values of ATP in the white matter at the point of failure of the cortical SEP. However, there was a marked reduction in the level of white matter PCr. In our previous work, the cortical SEP was abolished only when white matter ATP fell to critically low levels and this coincided with burst-suppression in the EEG in all cases. PCr was not measured. The result in the present experiment may have occurred because the rate of hemorrhage was carefully controlled over a two hour period in an effort to determine the earliest point at which the cortical SEP was abolished. In a majority of experimental cats, abolition of the cortical SEP occurred prior to the observation of burst-suppression in the EEG.

Our observation of a significant reduction in PCr without a change in ATP is similar to that seen following severe acute ischemia in cardiac and skeletal muscle. $^{31}$P NMR spectra of the human arm during thirteen minutes of tourniquet ischemia show marked reductions in PCr and elevations of inorganic phosphate (Pi) but a constant level of ATP. In myocardium, slow depletion of ATP follows the rapid loss of PCr and significant depletion of ATP corresponds to the onset of irreversible tissue damage. In contrast, studies of severe acute ischemia in brain have shown that PCr and ATP levels fall simultaneously and quickly. It has been suggested that the isoenzymes of creatine kinase in brain and muscle possess different activities or alternatively that not all of the ATP in brain is interconvertible with PCr stores so that ATP levels cannot be maintained as easily in brain as in muscle. Following normothermic circulatory arrest in rats, Norwood et al demonstrated that PCr and ATP levels in brain fall together whereas during hypothermic (20°C) circulatory arrest, PCr again falls rapidly without a change in ATP. In our experiment, hemorrhage over two hours produced a sub-acute ischemia. In this setting, as in hypothermic circulatory arrest, we

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**Table 1** ATP, Phosphocreatine (PCr), and Lactate (Lac) Levels from Five Experimental and Three Control Animals.

<table>
<thead>
<tr>
<th></th>
<th>Cortex</th>
<th>White Matter</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP</td>
<td>PCr</td>
<td>Lac</td>
</tr>
<tr>
<td>Control</td>
<td>2.02±0.28</td>
<td>3.99±0.62</td>
</tr>
<tr>
<td>Exp</td>
<td>2.13±0.35</td>
<td>3.28±0.92</td>
</tr>
</tbody>
</table>

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**Figure 2:** Comparison of the control and experimental levels of adenosine triphosphate (ATP), phosphocreatine (PCr), and lactate (Lac) in cortex and white matter. Experimental values were taken at the point of failure of the cortical SEP. Significant differences from control were observed in white matter PCr and in both cortical and white matter lactate. Values shown represent Mean ± SD.
hypothesize that the lower activity of brain creatine kinase is still adequate to maintain ATP by conversion from PCR and ADP. The availability of high field NMR spectrometers for in vivo chemistry will greatly facilitate our understanding of high-energy phosphate metabolism in brain.

In the present experiment, the cortical SEP was abolished even though ATP levels were not significantly altered. This makes it difficult to invoke energy failure as a cause for the dysfunction. However, Lowry et al. demonstrated that complete ischemia abolishes EEG activity within 10–15 seconds concurrent with PCR reductions of 30–50% but normal levels of ATP. Therefore, cerebral function may correlate more closely to levels of PCR than ATP. PCR is an immediate reserve of high-energy phosphate and could be more abolished even though ATP levels were not significantly reduced. If the generation of ATP from PCR was incomplete, the apparent dissociation between PCR reductions of 30–50% but normal levels of ATP would be undetected in macroscopic tissue samples. As a second explanation, elevated lactate might interfere directly with cerebral function. Glucose loading elevates brain lactate following ischemia and adversely affects post-ischemic recovery of other energy metabolites. Brain lactic acidosis has been found to impair posts ischemic recovery of the EEG and SEP. In our experiment, lactate levels in the white matter were only moderately elevated but could account for alteration of the SEP.

Focal cerebral ischemia due to arterial occlusion is the most common form of cerebrovascular insufficiency seen in clinical practice, resulting in a loss of function from direct injury to cortex. However, there are many clinical examples of ischemia in the end-field of arterial supply due to reduced perfusion pressures as appears to occur in the cerebral white matter in these experiments. Brain ischemia in infants may result in periventricular leukomalacia which has been ascribed to infarctions due to low flow in the territory between ventriculopetal and ventriculofugal end-arteries. In patients suffering infarction due to acute carotid occlusion, CT scan will often demonstrate infarction in the white matter with sparing of the cortex, so-called terminal-zone infarction. These observations are evidence that selective failure of white matter perfusion is not uncommon in the clinical setting. Alterations of the SEP in these situations probably reflect ischemia in the conduction pathways as we observed in our experiments and require a fundamentally different interpretation than in focal cerebral ischemia.

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References

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