THREE PAPERS in this issue of Stroke highlight the use of short latency somatosensory evoked potentials (SEPs) to quantify neuronal dysfunction in models of cerebral ischemia. These investigators, and others, have taken advantage of two special properties of SEPs, and "early" EPs in general: a relative resistance to general anesthesia, and an approximate localization of cortical SEP generators to the somatosensory cortex, (or the ectosylvian gyrus in animals), allowing correlation of electrical activity with local CBF. Unfortunately, this literature is arduous reading, even for the initiated. Because SEPs are likely to be used more often to validate models of ischemia and to study stroke patients, it is important to understand the technical difficulties, to appreciate the care required for a dependable result, and to recognize the limitations on interpretation, especially in ischemia.

Technical Matters

Comparing data from different experimental models is difficult because of widely varying methods; in addition there are significant problems inherent in measuring electrical phenomena in ischemic tissue. Animal species and stimulus sites differ, but the models reported in this issue have been used previously by others. In cats, the first major negativity thought to be generated from the cortex after median nerve stimulation has had an absolute latency of 10.8 msec, 11.4 msec, 2 12 msec, 12.5 msec (Coyer et al in this issue), or 13.2 msec. 4 Presumably, these are all the same potential but the latency differences demonstrate how technical aspects of stimulation and recording influence results. Interpretation of published material therefore requires information on at least: Stimulus site, intensity, and frequency; Number of repetitions; Amplifier bandpass; Filters; Polarity; Recording derivations; and Waveform reproducibility (replication). Unretouched SEP tracings with wave peaks labelled and calibration markers are also essential in judging the quality and comparability of the work. Research using middle (30–75 msec) or long latency (>75 msec) EPs (as opposed to the short latency studies) must be interpreted cautiously because later waves are less reproducible and subject to greater variation with minor changes in technique and physiologic state.

The technical aspects of the three papers in this issue compare favorably to much of the existing literature. McPherson’s description of SEP technique is exemplary; the others omit some data such as stimulus frequency, intensity, and reproducibility during the pre-ischemic period, but the material is generally interpretable. The amplitudes of the cortical SEP reported in publications using similar techniques in the same animal vary so widely that authors have resorted to using percentage change from control amplitude and pooling data in order to quantify amplitude changes during ischemia. The comparability of results in the literature is further limited because some report SEP latency, others amplitude, and a few, both. The timing of SEP recording with respect to the onset of ischemia is particularly important if latency is considered.

There are potential problems arising from the conducting properties of ischemic tissue and difficulties with recording SEPs during brief and rapidly changing periods of ischemia. The surface recorded SEP is the sum of local electrical activity and volume conducted potentials from adjacent regions. Ischemic tissue has increased impedance, in part accounting for a diminished SEP amplitude. (There are theoretical reasons why this cannot be the whole explanation). Branston has observed that stimulation of the somatosensory pathways at high rates itself increases cortical blood flow slightly, probably by placing increased metabolic demands on the active neurons. 5 Compounding these problems is the inability to record more than one brief trial of SEPs because CBF measurements must be almost simultaneous in order to make correlations. The polarographic hydrogen clearance technique tends to be less accurate at the low levels of CBF required to alter the SEP, further reducing the certainty of CBF results. Producing a meaningful SEP during ischemia is difficult, demands technical expertise, and great care in interpretation. CBF thresholds related to SEP changes may have only limited precision.

Nomenclature

Waves generated by subcortical structures are more resistant to ischemia than those from the cortex. 2 6 Enough experimental work has been done in animals for most workers to agree tentatively that the first major wave recorded from the scalp is generated by cortical neurons. Animal and human electrophysiology have not always been identical; the negativity in man is thought by some to be generated in the thalamus. Cortical waves in some animals have positive polarity but are equivalent to the N19-P22 (N20) of the median nerve SEP in humans. In cats, however, the important cortical potential for median nerve stimulation has been called P2-MN 1 or Wave V 3,4 used by Coyer et al. It would be helpful if investigators labelled waves by polarity and time of appearance in milliseconds, and displayed an upward deflection for negativity at the active electrode.

CBF and the SEP

Meldrum and Brierly in 1969 7 were the first to suggest exploiting SEPs for ischemia research. In the last decade, the extensive and careful work of Branston and Symon's group, 3 6 8 9 has delineated the relationship between CBF and SEP. Most previous work, including theirs, suggests that the amplitude of cortical SEP waves is most closely associated with ischemia; latency changes are more variable. In the first several minutes of ischemia cortical SEP latency has varied with CBF over a wide range of decreased blood flows (15–50 ml/100 gm/min), but then has remained un-
Meaning of SEPs in Ischemia

The looming problem in this research is uncertainty about the relationship of the ischemic threshold for SEPs, approximately 12–18 ml/100 g/min, and cerebral infarction. Persistence of SEPs does not assure the absence of infarction, though there is a tendency for larger infarcts to cause greater reductions in SEP latency. In addition, a simple ischemic threshold for the SEP gives an incomplete idea of the mechanism of stroke; the all important element of duration of ischemia has not been studied with SEPs.

Why does the SEP disappear as neurons become ischemic? In experimental models of ischemia we assume that coupling of CBF and metabolism persists. McPherson’s paper in this issue makes a nice contribution by demonstrating that the SEP diminishes and recovers in parallel with metabolic impairment (CMR02) of brain tissue, regardless of CBF or cerebral oxygen availability. Unfortunately, both blood flow and CMR02 were global measurements, so the precise effects of hypoxia on SEP pathways remained unknown. They did observe SEP amplitude was decreased to less than 20% of control when the EEG was flat or showed burst suppression.

Another group has found that prolonged latency of cortical SEP waves correlated with white matter, not grey matter, ischemia and the cortical SEP was abolished only when white matter CBF and ATP fell to critical levels. Some animals had reduced SEP amplitude with normal cortical CBF. With further reduction in flow the cortical wave was lost when white matter ATP became totally depleted, while energy levels in the cortex remained high. More meaningful indicators of irreversible neuronal damage; failure of the Na/K pump and membrane depolarization, occur at even lower levels of flow than required to abolish the SEP. CBF persistently below 10 ml/100 g/min is necessary for potassium efflux from cells and cell death. Therefore, the truly “lethal” flow threshold for stroke is below the level that completely suppresses the SEP. Maintaining CBF above 12 ml/100 g/min for prolonged periods produced no histological changes in the cortex in one experimental model, and both energy state and ion homeostasis have been restored after prolonged ischemia in this range. Astrup et al, in a 1981 editorial, summarized current concepts of flow threshold for infarction and suggested that loss of electrical function at 12–18 ml/100 g/min might be a protective sacrifice by neurons. Whatever the precise level and duration of ischemia associated with stroke, changes in the SEP do not directly reflect the fundamental pathophysiologic mechanisms causing cerebral infarction; they are only markers of reduced CBF.

The most intriguing feature of SEPs, similar to the EEG, may be the contrast between resistance to anesthesia, and sensitivity to ischemia. Anesthetics (and hypothermia) are unique in producing coma and greatly decreased cerebral metabolic rate without structural damage. Until recently, anesthetics were thought to suppress most neurophysiologic activity in parallel, as reflected by the EEG. Anesthesia may spare the ability of neurons to respond to an electrical volley, or more likely, it may specifically suppress the diencephalic drivers of EEG activity.

Suggestions

SEPs as research tools have potential drawbacks, but when performed carefully under controlled circumstances they promise to teach us much about the ischemic brain. Even with their modest limitations, an improvement in SEP amplitude resulting from therapy for ischemia would be convincing evidence of benefit. When used haphazardly, simply to legitimize an experimental model, as evidence of infarction, or as reflecting some primary function of the sensory system, they only add to the existing confusion. I would make a plea for more uniformity in stimulus and recording technique, nomenclature, and above all, interpretation. The ability of SEPs to reflect neuronal function is impressive, but conclusions about ischemia based predominantly on SEPs can be misleading; at the moment these experiments tell us as much about SEPs as they do about ischemia.

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Evoked potentials in cerebral ischemia.
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*Stroke*. 1986;17:3-5
doi: 10.1161/01.STR.17.1.3

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1986 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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