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Cerebral microdialysis combined with single-neuron and electroencephalographic recording in neurosurgical patients

Technical note

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✓ Monitoring physiological changes in the brain parenchyma has important applications in the care of neurosurgical patients. A technique is described for measuring extracellular neurochemicals by cerebral microdialysis with simultaneous recording of electroencephalographic (EEG) and single-unit (neuron) activity in selected targets in the human brain. Forty-two patients with medically intractable epilepsy underwent stereotactically guided implantation of a total of 423 intracranial depth electrodes to delineate potentially resectable seizure foci. The electrodes had platinum alloy contacts for EEG recordings and four to nine 40-μm microwires for recording single-unit neuron activity. Eighty-six electrodes also included microdialysis probes introduced via the electrode lumens. During monitoring on the neurosurgical ward, electrophysiological recording and cerebral microdialysis sampling were performed during seizures, cognitive tasks, and sleep–waking cycles. The technique described here could be used in developing novel approaches for evaluation and treatment in a variety of neurological conditions such as head injury, subarachnoid hemorrhage, epilepsy, and movement disorders.

KEY WORDS • depth electrodes • epilepsy • memory • microdialysis • single neuron

Over the past decade considerable advances have been made in the noninvasive preoperative evaluation of candidates for epilepsy surgery, including video-electroencephalographic (EEG) monitoring and the application of neuroimaging techniques such as magnetic resonance (MR) imaging, positron emission tomography, and single-photon emission computerized tomography scanning.[10] Despite these advances there is still a subset of patients who require further monitoring with intracranial electrodes to delineate a potentially resectable epileptogenic zone. After electrode placement, patients are usually monitored for a period of 1 to 2 weeks until a sufficient number of spontaneous seizures are recorded. The information collected using the electrodes is typically limited to regional EEG signals, which reflect the activity of large neuronal populations. However, the presence of a probe within the brain parenchyma offers the opportunity to gather additional data on several levels of neuronal function.

A neurological event such as a seizure is accompanied by robust changes, not only in the sum electrical activity of neuronal populations but also in the activity of single cells and in the concentration of neuroactive substances in the extracellular milieu.[1,4,6,8,31,38] Such changes may have clinical implications. For instance, excessive excitatory amino acid release during seizures may be associated with excitotoxicity,[2,5,24,27] and changes in biogenic amines may signal transitions between different states of consciousness in patients with head injury or other neurological problems. To maximize the information obtained through intracranial electrodes, we have developed a probe that records intracranial EEG readings while at the same time enabling recording of the activity of single neurons and sampling of the extracellular fluid by cerebral microdialysis. We demonstrate the feasibility of using this technique to characterize changes in the neuronal parenchyma of neurosurgical patients during seizures and other behavioral states.

Monitoring Technique

Patient Population

Between January 1993 and March 1998, 42 patients (21 males and 21 females; mean age 33.2 years; range 12–50 years) with pharmacologically intractable seizures underwent implantation of intracranial depth electrodes. All surgeries were performed by the same surgeon (I.F.). Because these patients suffered from pharmacologically resistant chronic seizures, they were being evaluated as candidates for epilepsy surgery. In all these cases extensive noninvasive workups did not yield concordant data pointing to a single resectable focus of the disease; therefore, invasive monitoring was subsequently conducted via in-

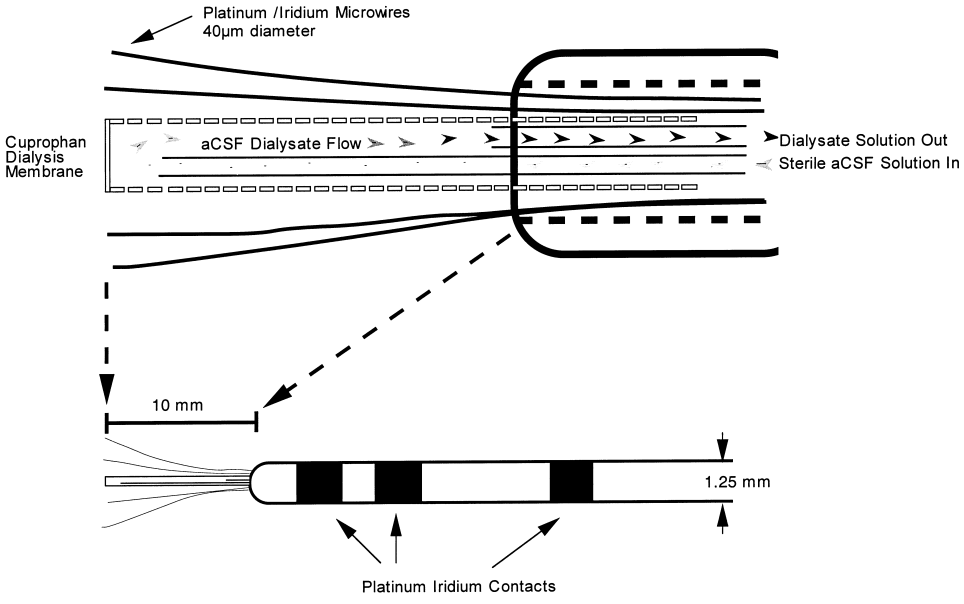

FIG. 1. Diagram of flexible probe used for concomitant recording of EEG and single-unit activity and for cerebral microdialysis. Low magnification *(lower)* shows the platinum contacts for EEG recordings. The upper part of the illustration is a magnification of the distal part of the probe, showing inflow of aCSF and outflow of the dialysate, as well as the cuprophan membrane through which substances in the extracellular fluid migrate along a concentration gradient into the probe. At the distal end is the membrane of the microdialysis probe and four platinum-iridium microwires used for single-unit recordings.

tracranial depth electrodes. All studies described here were performed according to the guidelines of the Medical Institutional Review Board at the University of California at Los Angeles.

Electrode Characteristics

The electrodes (Fig. 1) consisted of MR imaging–compatible, flexible, polyurethane probes with six or seven 1.5-mm-wide platinum contacts with intercontact separations of 1.5 to 4 mm. These contacts enable EEG recording at various sites along the electrode trajectory. In addition, the lumen allows insertion of 40-µm heavy formvar–insulated platinum/20% iridium microwires. The microwires (with impedances ranging from 200–800 kOhms) are capable of resolving the activity of multiple or single-unit neurons. Typically, four to nine microwires are inserted, extending 4 to 5 mm beyond the tip of each microelectode. The microdialysis probe (Fig. 1) is introduced through the same lumen and consists of a cuprophan microdialysis membrane (200 ± 15–µm diameter). Two fused silica tubes contained within the membrane are used for inflow and outflow, respectively, of the dialysate (inflow: outer diameter [OD]/inner diameter [ID] = 105/40 µm, length = 39 cm; outflow: OD/ID = 150/75 µm, length = 39 cm, connected to the fraction collector with fused silica tubing; OD/ID = 375/150 µm, length = 120 cm).

Surgical Procedures

Electrodes were placed stereotactically with MR imaging and angiographic guidance. Before surgery each patient underwent placement of a stereotactic headframe, and then a detailed MR image was obtained using a spoiled-gradient sequence, followed by cerebral angiography. Both MR and digital subtraction (DS) angiography images were transmitted to a workstation in the operating room, and surgical planning was then performed, with selection of appropriate temporal and extratemporal targets and appropriate trajectories based on clinical criteria. Special attention was given to the venous phase of the angiogram so that the cortical surface veins could be avoided at the chosen trajectories. A dynamic multiimage environment permits simultaneous display of MR and DS angiography images, with rapid viewing of potential trajectories in different planes before the final selection is made. The patient was then taken to the operating room and general anesthesia was induced, after which multiple electrodes were placed, usually bilaterally and orthogonally from lateral to medial. At each entry point, a twist-drill hole was made, the dura was coagulated and punctured, and a screw guide was inserted into the bone. The electrode was then introduced with a stylet through the guide screw to the correct depth, the stylet was withdrawn, and the microwires with the microdialysis probe were introduced through the lumen of the electrode. Finally, a cap was secured over the guide screw to prevent cerebrospinal fluid (CSF) leakage. This procedure was repeated for each electrode.

Following electrode placement the patients were monitored in a special unit on the neurosurgical ward for a period of 1 to 3 weeks, until a sufficient number of spontaneous seizures had been recorded. Prior to removing the electrodes, MR images were obtained to confirm their location (Fig. 2). The patient was then given a local anesthetic and the electrodes and guide screws were removed.

Electroencephalographic and Single-Unit Recordings

Continuous video-EEG monitoring from the 1st post-

operative day was performed (sampling frequency 200 Hz; EEG frequency bandpass 1–70 Hz). Single-unit activity was recorded via six bundles of microwires connected to a miniature jackpanel, which was attached to a 16-channel preamplifier module, providing a gain of 5000 over a bandpass of 0.3 Hz to 6 kHz. Wide-band EEG activity (0.1 Hz–10 kHz) from each microwire was high-pass filtered (300 Hz–10 kHz) to allow stable triggering of action potentials above background noise. Using commercially available software, 2 msec of electrophysiological activity surrounding each triggered action potential was digitized at 20 kHz, and multiple units were separated on the basis of action potential amplitude, duration, slope, and other parameters of waveform morphology.[23]

Microdialysis Procedures

Sterile phosphate-buffered artificial (a)CSF (125 mM NaCl; 2.5 mM KCl; 0.5 mM NaH_2PO_4; 5 mM Na_2HPO_4; 1.2 mM $CaCl_2$; 1 mM $MgCl_2$; 0.2 mM ascorbic acid; pH 7.3–7.4.) was perfused through the probes at a flow rate of 1.2 μl/minute. Sterile, disposable plastic 3-ml syringes were used for aCSF delivery, driven by a pair of minipumps with direct-current motors to reduce electrical noise affecting the microelectrode recordings. Flow was established before placement of the microdialysis probes in the brain and maintained during application of the head dressing, in the recovery room, and on the neurosurgery ward, where samples were collected every 30 minutes, using an automated fraction collector. When a seizure occurred, the collection period was immediately reduced to 5 minutes. The dead space in the collection tubing allowed for collection of four 5-minute preseizure samples. In some cases in which there were multiple seizures, continuous 5-minute samples were taken. Similarly, the sampling interval was reduced to 5 or 10 minutes during cognitive tasks. Samples were stored at −80˚C prior to analysis.

Amino Acid Analysis. Brain dialysate samples were analyzed using a high-performance liquid chromatography (HPLC) fluorometric detection procedure for quantitation of amino acids as previously described.[38] The amino acids were derivitized with *o*-phthaldehyde (OPA) before automatic injection onto the HPLC column. The OPA-derivitizing agent was prepared by adding 40 μl OPA (100 mg/ml methanol) and 5 μl β-mercaptoethanol (1% vol/vol in 0.0125 M boric acid buffer, pH 10) to 3.95 ml of 0.125 M boric acid buffer, pH 10. An aliquot of OPA reagent equal to twice the volume of the sample was reacted with the sample for 30 seconds. The OPA–amino acid adducts were resolved on a reversed-phase 3 × 150–mm column with sodium acetate (35 mM, adjusted to pH 5.9 with glacial acetic acid), 1% vol/vol tetrahydrofuran and 0.01% vol/vol tetraethylamine as aqueous solvent. The organic mobile phase contained 70% acetonitrile, 15% methanol and 15% sodium acetate (35 mM final concentration), adjusted to pH 7.65 with glacial acetic acid. The flow rate was 0.6 ml/minute, with a gradient profile as follows: 10.5 to 15% in 3 minutes, held at 15% for 3 minutes, and 15 to 33% in 9 minutes. The column was washed with a gradient of 33 to 65% in 0.5 minutes, held at 65% for 2 minutes, and returned to 10.5% in 0.5 minutes. The column was equilibrated at 10.5% for 5 minutes before injection of the next sample. The limit of detection was 20 fmol.

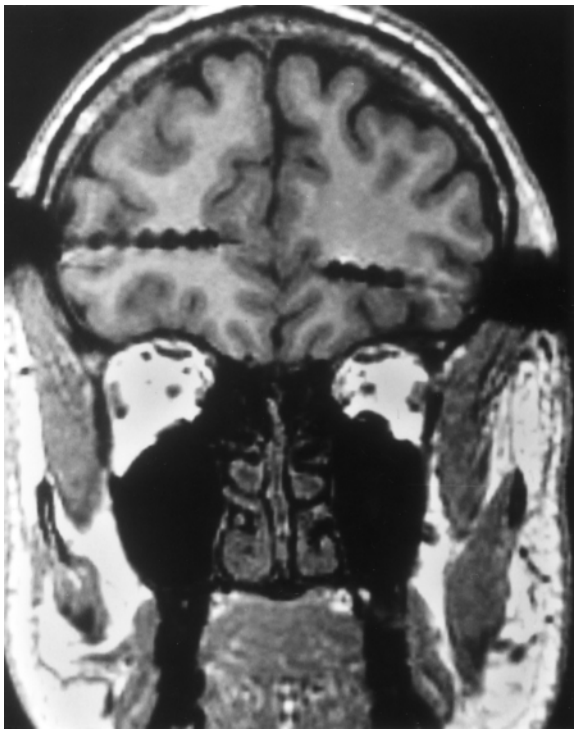

FIG. 2. Coronal MR image (spoiled-gradient sequence on 1.5-tesla imager) demonstrating intracranial depth electrodes placed in the ventromedial frontal cortex of a patient with epilepsy. The contacts for EEG recording along the shaft of each electrode create an MR artifact that is larger than the actual diameter of the probe (1.3 mm). The guide screws at the entry sites also create MR artifacts that are considerably larger than the twist-drill hole used for placement of each electrode. The distal end of the electrode on the right side includes a microdialysis membrane and platinum-iridium microwires, whereas the distal end of the electrode on the left side includes only microwires.

The whole procedure, including data collection and calculation, was completely automated using commercially available hardware and software.

Biogenic Amine Analysis. For determination of norepinephrine, dopamine, and serotonin in dialysates, HPLC with electrochemical detection was used. All three amines were separated in the same run, with retention times of approximately 4, 8, and 11 minutes, respectively. The mobile phase consisted of: sodium acetate (75 mM), sodium dodecane sulphonate (0.75 mM), ethylenediamine tetraacetic acid (10 μM), triethylamine (0.01%), acetonitrile (12%), methanol (12%), and tetrahydrofuran (1%), pH 5.5, pumped at a rate of 200 μl/minute through a 100 × 2–mm column. The system was calibrated at regular intervals and provided a limit of detection of approximately 0.1 fmol.

Electrophysiological recordings and microdialysis sampling were performed during seizures, during cognitive tasks, and during waking and sleep states. Sleep staging was scored using the criteria of Rechtschaffen and Kales.[30]

Sources of Supplies and Equipment

The electrodes were purchased from AdTech, Racine, WI, and the microwires from California Fine Wire, Grover Beach, CA. The microdialysis membrane was from

TABLE 1

*Distribution of probes with and without microdialysis capability according to brain sites of placement**

Site	EEG & Single-Unit Only	EEG, Single-Unit, & Microdialysis
amygdala	37	38
hippocampus	90	33
entorhinal cortex	52	2
posterior PHG	34	2
orbitofrontal cortex	47	9
supplementary motor area	21	0
cingulate cortex	40	2
other	16	0
total	337	86

* Hippocampus placement included sites in the anterior (71), middle (39), and posterior hippocampus (12), and one site in the presubiculum. Abbreviation: PHG = parahippocampal gyrus.

Akza Nobel Faser AG, Wuppertal, Germany. The fused silica tubing was obtained from Polymicro Technologies, Inc., Phoenix, AZ. The stereotactic headframe (Leksell, model G) was purchased from Elekta, Atlanta, GA, and the MR imager (Signa 2) from General Electric, Milwaukee, WI. The workstation used in surgical planning was obtained from Silicon Graphics, Mountain View, CA.

The seizure detection and monitoring systems (Nicolet/BMSI 5000 and Telefactor) were obtained from Nicolet, Madison, WI, and Telefactor, Conshohocken, PA, respectively. The software used to digitize the triggered action potentials (Data Wave Experimenter's Workbench) was acquired from Data Wave, Longmont, CO. The minipumps (model CMA-102) used for aCSF delivery, the automated fraction collector, and the HPLC autoinjector were purchased from CMA, Stockholm, Sweden. The HPLC resin columns (Hypersil, 3 μm, C18) were obtained from Keystone Scientific, Bellefonte, PA. Automated data collection and calculation for amino acid analysis were performed with the aid of Gilson hardware and software, Gilson, Middleton, WI. The HPLC system with electrochemical detection (Antec) can be purchased from GBC Separations, Hubbardston, MA. The Shimadzu pump (model LC-10AD) used for the mobile phase delivery of the biogenic amine analysis was acquired from Cole Scientific, Moorpark, CA.

Results

Clinical Procedures

A total of 423 electrodes carrying a total of 3377 microwires was placed stereotactically in 42 patients. The criteria for placement of intracranial electrodes and the procedures for EEG and video monitoring at the University of California at Los Angeles are part of routine protocols that have been described in previous publications.[9,12] The number of electrodes per patient varied from six to 14. Eighty-six of these electrodes included microdialysis probes in addition to the EEG contacts and the microwires. The remaining electrodes had only EEG contacts and nine microwires each. In Table 1 the distribution of electrodes is described according to sites of placement. The choice of placement sites was dictated by the questions pertaining to the suspected regions of epileptogenesis. These included questions of lateralization and/or localization within one side. In most patients electrodes were placed bilaterally because there was some question as to the side of seizure origin, and in many patients there was also a question of whether the seizures were of frontal or temporal origin. If frontal seizures were suspected, electrodes were placed in one or more of the following locations: orbitofrontal cortex, cingulate cortex, and supplementary motor area.

Single-Unit Recording

Typically, six to 20 single units were resolved from recordings in each patient. The single-unit signals sometimes changed during the course of monitoring, reflecting the gradual deterioration of the signal, but excellent recordings were usually obtained from Days 2 through 6 after placement of the electrodes. Although EEG recordings of seizure activity were easily obtained (Fig. 3), single-unit recordings from the microdialysis probes have often been difficult to resolve because of multiplexer noise, but this problem has been greatly reduced with modifications of the monitoring equipment. Figure 4 depicts an example of single-unit recordings from an electrode combining microdialysis probe and microwires. In this recording at least two units can be resolved based on amplitude.

Single-unit recording was also accomplished during spontaneous seizures and was easily obtained during cognitive tasks and sleep stages. Single-unit signals with increased or decreased rates of firing were identified during

FIG. 3. Bilateral EEG recordings from mesial temporal lobe structures in a patient with epilepsy. The seizure first developed in the right mesial temporal lobe but rapidly spread to the left side. Each interval between adjacent vertical lines depicts 1 second of recording. Recording sites were referred to a scalp lead at the central vertex position (C2) with negativity up. LA = left amygdala; LAH = left anterior hippocampus; LEC = left entorhinal cortex; RA = right amygdala; RAH = right anterior hippocampus; REC = right entorhinal cortex; RMH = right midhippocampus.

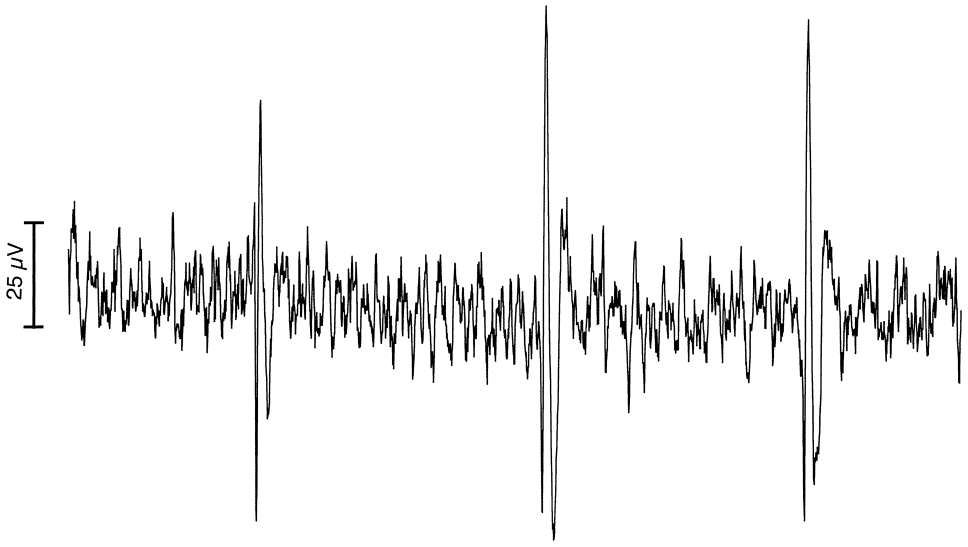

FIG. 4. Single-unit recording from an electrode combining a microdialysis probe and microwires that was placed in the right anterior hippocampus of a patient who had intractable seizures. This recording obtained from a single microwire shows a 200-msec sweep, with action potentials originating from at least two different neurons, which can be appreciated here by the different amplitudes of the action potentials. Positivity is up in reference to an uninsulated microwire 5 mm away.

seizures, but movement artifacts during the later behavioral phase of seizures often obscured single-unit recordings. During cognitive tasks single-neuron activity can be recorded during selected phases of the task and time locked to presentation of stimuli.[11,26] Figure 5 shows the rasters and frequency histograms for two hippocampal neurons during a delayed nonmatch-to-sample task, in which the patient is presented with a stimulus followed by two distractors and then asked to identify which of two stimuli had not been presented before. Both neurons had increased activity during the delay (when distractors were presented) and the subsequent choice. Figure 6 shows the activity of two neurons during reading and working memory tasks. Both neurons, located in the right presubiculum, demonstrated decreased firing rates during the two memory task segments compared with the reading task.

The presence of microwires in the parenchyma enables simultaneous recording of field potentials and single units to yield complementary information. The activity of single neurons recorded through the same microwire can be distinguished once the time scale is expanded. This technique is illustrated by recordings taken during different stages of sleep, as in Fig. 7, which shows single-unit and EEG activity in the left entorhinal cortex at 3 Hz during slow-wave sleep (Stage 4).

Microdialysis Sampling

A total of 86 microdialysis probes were implanted in 28 patients. The distribution of the probes according to anatomical sites is shown in Table 1. We have used microdialysis sampling to measure extracellular concentrations of

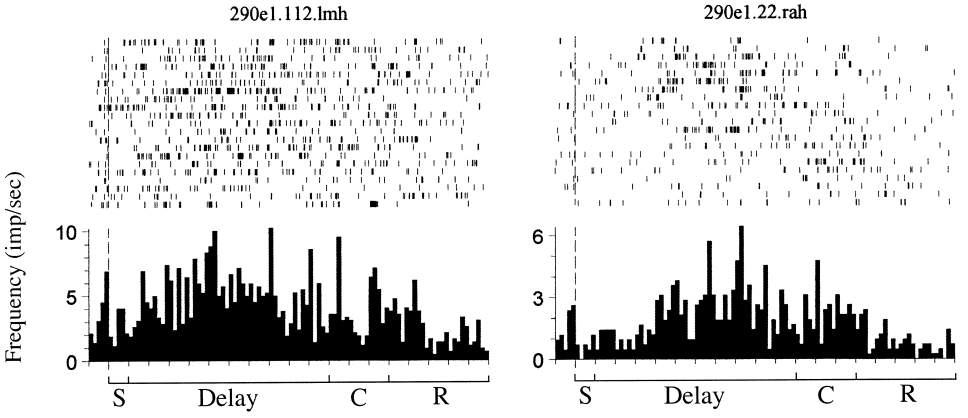

FIG. 5. Rasters *(upper)* and histograms *(lower)* of two single neurons in the left middle hippocampus (290e1.112.lmh; *left*) and the right anterior hippocampus (290e1.22.rah; *right*) recorded simultaneously during the delayed nonmatch-to-sample task (see *Single-Unit Recording* for detailed description of the task). Note the increase in the firing rate of each neuron during the delay period of the task. *Vertical broken line* depicts onset of the stimulus. Each *horizontal line* in the rasters represents firing of the neuron during a single trial. C = choice; imp/sec = impulses per second; R = response; S = stimulus presentation.

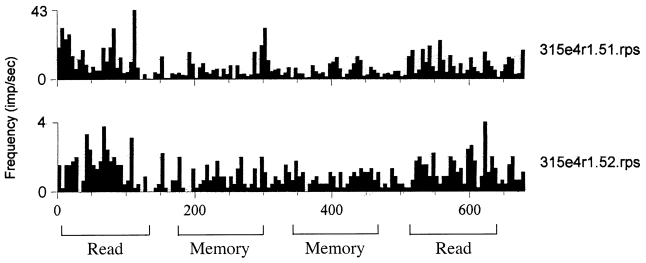

FIG. 6. Rate histograms showing firing rate (imp/sec) for two units in the right presubiculum (rps) recorded via a single microwire during reading and memory tasks (x axis depicts seconds). In the reading task the patient read a list of words, each presented for 1 second with a 2- to 4-second interstimulus interval. In the memory task a similar list was used, but the presentation of each word served as a cue for the patient to say the word shown in the previous trial. Note the decrease in unit activity during the memory task compared with the reading task.

amino acids and monoamines. Although there was a gradual decline in the baseline levels of these substances over time, samples with detectable levels were obtained throughout the first 6 days of monitoring. An example of monitoring amino acid concentrations by microdialysis in consecutive 5-minute samples is illustrated in Fig. 8. During one of the 5-minute sample periods a seizure occurred. The EEG tracing of the seizure is depicted in Fig. 3, showing seizure onset in the right mesial temporal lobe contacts (hippocampus, entorhinal cortex, and amygdala). A concomitant rise in the levels of the excitatory amino acids glutamate and aspartate, as well as the inhibitory amino acids taurine and γ-aminobutyric acid (GABA), was seen in the right amygdala, but not in the left, in the 5-minute sample collected during the seizure.

A comparison of GABA levels in the right and left amygdala is shown for the same patient during two consecutive seizures (Fig. 9). In this particular case 5-minute sampling was performed over several hours. Typically, however, samples were collected every half hour and the collection time was only reduced to every 5 minutes at the onset of a seizure. Because of the dead time of approx-

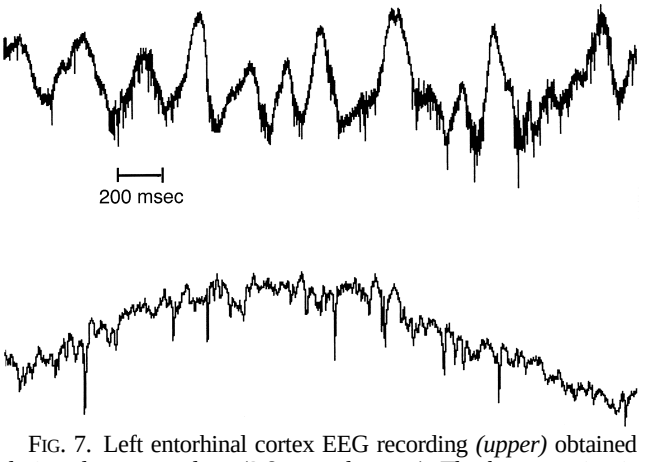

FIG. 7. Left entorhinal cortex EEG recording *(upper)* obtained during slow-wave sleep (2.8-second sweep). The *lower* tracing is the expanded 200-msec segment of the field potential indicated by the bar just below the *upper* tracing. It shows single units recorded through the same microwire.

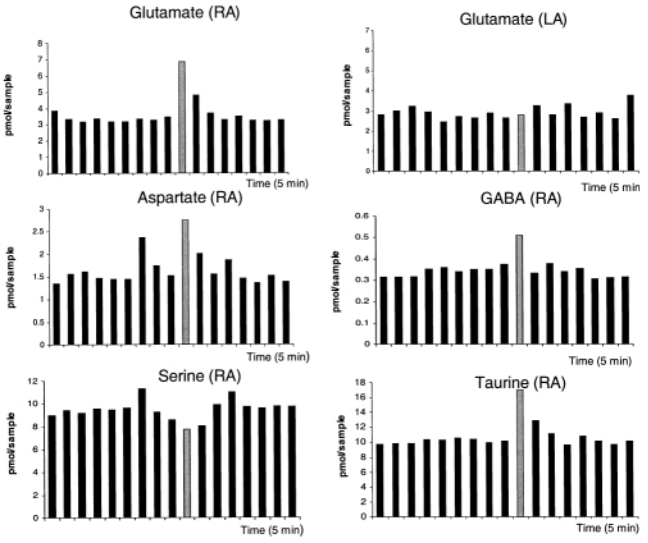

FIG. 8. Histogram showing changes in the extracellular levels of amino acids measured by microdialysis in the right amygdala (RA) during a seizure. Microdialysis sampling was performed every 5 minutes, and the levels found during the seizure are indicated by the *gray bars*. Note increased dialysate concentrations of glutamate, aspartate, GABA, and taurine (but not serine) in the right amygdala. The glutamate level in the left amygdala (LA) did not change. The EEG recording for this seizure is shown in Fig. 3. The seizure first involved the right mesial temporal structures, including the right amygdala, but rapidly spread to the other side.

imately 20 minutes during which the solution travels through the tubing to the fraction collector, the initial 5-minute fraction contains dialysate obtained 15 to 20 minutes before the seizure.

Figure 10 shows the levels of several amino acids in the hippocampus of a patient during a delayed nonmatch-to-sample memory task of words and faces and during rest periods (the task was the same as that described in the text in *Single-Unit Recording* relating to Fig. 5). In this case the task is sustained for 10-minute samples, a sufficient duration to detect an increase in the levels of aspartate and glutamate during the first memory task. Analysis of biogenic amines is illustrated in Fig. 11, which shows changes in the norepinephrine level in the hippocampus during the memory and reading tasks with intervening periods of rest (the same tasks as described in Fig. 6).

Complications of the Procedure

The only complication in the series was in a single patient in whom a small (1-cm) pocket of air and fluid was detected at one electrode site on a routine postoperative MR image. There were no adverse neurological signs. This problem was traced to a possible break in the EEG macroelectrode, and subsequently a small change in the design was made to reinforce this part of the electrode.

Discussion

There are distinct neurosurgical settings in which detailed information about the local brain parenchyma can provide useful data in evaluating the status of the patient. Some patients with pharmacologically resistant epilepsy

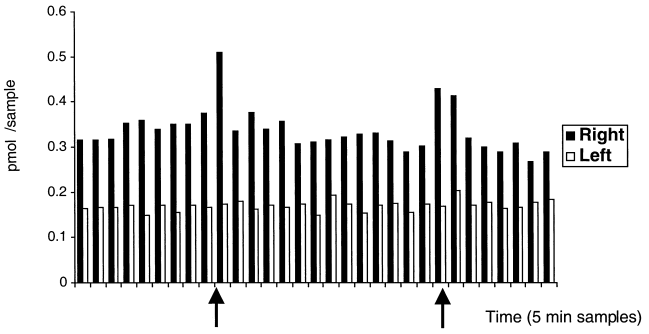

FIG. 9. Histogram showing changes in the extracellular levels of GABA measured by microdialysis in the right and left amygdala during two consecutive seizures *(arrows)* involving the right amygdala first but rapidly spreading to the left amygdala. Five-minute samples were collected continuously over several hours. Note increased GABA concentration in the dialysates from the right amygdala, restricted to the periods of the seizures.

have a resectable epileptogenic focus that cannot be localized and characterized by noninvasive methods. The technique described here provides an opportunity to obtain diverse types of information at various levels of neuronal function simultaneously. The EEG recording provides a summation of neuronal activity in large neuronal populations, whereas single-unit recording provides information on the activity of individual neurons. The microdialysis technique samples the extracellular fluid in situ from a limited area, allowing measurement of neuroactive substances such as amino acids and biogenic amines. In planning the application of these techniques it is important to take into consideration their temporal resolution. Whereas EEG and single-unit recordings have millisecond resolutions, cerebral microdialysis has a temporal resolution on the order of minutes. We have not collected samples for less than 5 minutes because of the difficulty in detecting amino acids and monoamines in smaller samples. Using longer collection times per fraction for events of short duration, such as seizures, poses the risk of diluting changes in neuroactive substances.

There are additional methodological factors to be considered when using the microdialysis technique in a clinical setting. Some trauma is associated with the initial insertion of the probe, and it has been suggested that substances recovered initially in the dialysate represent leakage from damaged tissue.[14] However, studies have shown that after a few hours basal levels of neuroactive substances become stable in both anesthetized and conscious animals.[3,14,15] We have therefore not used samples obtained in the first 24 hours after probe insertion. In agreement with animal studies, we found that baseline levels decrease over the duration of the monitoring period (approximately 1–2 weeks). This may be caused by parenchymal changes such as gliosis around the probe tip, although animal studies have shown that such neuropathological changes are minimal and should not interfere with local brain metabolism.[37] Such changes probably influence the yield of single-unit recording as well: after 5 to 7 days there is usually a drop in the number and amplitude of single units observed, but no changes in the EEG data. Therefore microdialysis sampling and single-unit recording were usually performed from the 2nd through 6th

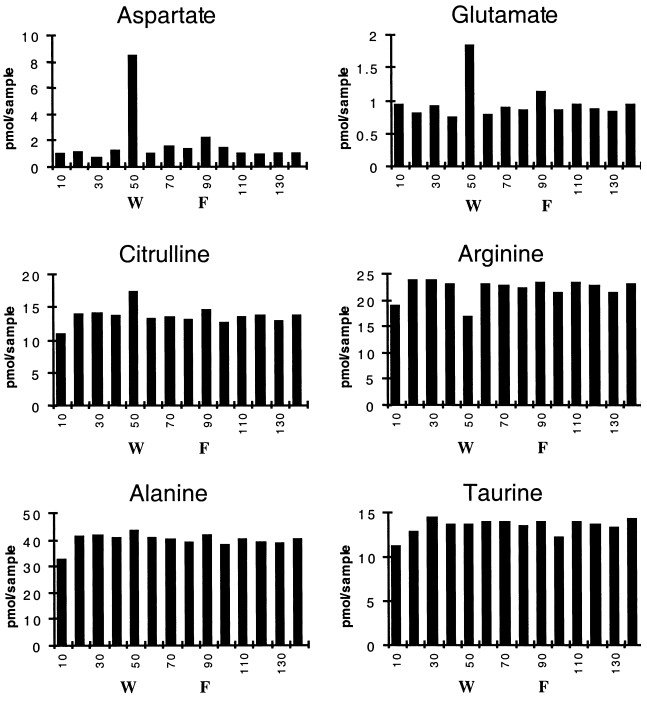

FIG. 10. Histograms showing extracellular amino acid levels measured by microdialysis in the hippocampus during performance of the delayed nonmatch-to-sample task (same task as in Fig. 5). Continuous 10-minute samples were collected. The task periods are marked by a W (words used as stimuli) and an F (faces used as stimuli).

postoperative days. During this time period we were able to detect amino acids and monoamines in the samples. In determining changes in dialysate concentrations of neuroactive substances as well as changes in firing rates of single units, comparisons were always made against the immediately preceding baseline, and never across days of monitoring. However, determinations made across longer intervals need to take into account these baseline changes; for example, in monitoring the clinical course of patients with head injury.

The microdialysis technique has been coupled with intracranial depth electrodes by During and Spencer,[8] who demonstrated changes in amino acids, specifically glutamate and GABA, during seizures. The electrodes used by these authors differed from our design in several ways.

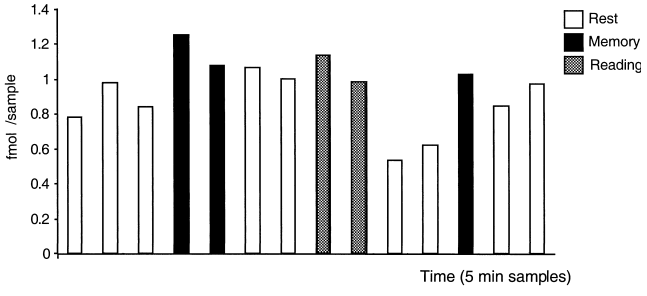

FIG. 11. Histogram showing extracellular norepinephrine levels measured in the right hippocampus by microdialysis for 5-minute periods during reading and memory tasks and intervening periods of rest.

First, their electrodes did not incorporate microelectrodes for single-unit recordings. Second, the microdialysis membrane was 4 cm long (compared with 1 cm in our electrodes), limiting the spatial resolution of the measurements. The electrodes were introduced occipitally through the long axis of the hippocampus, so that the distal end of the electrode was often in the amygdala. Such electrodes do not enable exclusive sampling of the amygdala or subregions of the hippocampus.

In recent years there has been increasing use of the microdialysis technique in a variety of neurosurgical clinical settings, most notably in patients with head injury and subarachnoid hemorrhage (SAH).[16,28,29] Cerebral pH[19] and temperature[25] and levels of several chemical substances can now be monitored online by using microdialysis, thus providing rapid feedback.[8,22,28] The coupling of the microdialysis technique with EEG monitoring is advantageous, as there are distinct EEG changes that reflect the clinical state of neurosurgical patients in the intensive care unit. For example, Vespa, et al.,[35] have shown increased incidence of nonconvulsive seizures in patients with head injury. Such seizures are not routinely detected unless continuous EEG monitoring is undertaken. Periods of nonconvulsive and convulsive seizures in these patients may be accompanied by changes in neuroactive substances such as glutamate, which may indicate neurotoxicity and cell death.[33] Concomitant EEG recording and microdialysis sampling in this setting might be advantageous. Vespa, et al.,[34] have also demonstrated early detection of vasospasm after acute SAH by using continuous EEG monitoring in the intensive care unit. Persson, et al.,[29] have shown a correlation between the extracellular fluid levels of glutamate and outcome in patients with SAH. The ability to obtain intraparenchymal EEG recordings concurrently with sampling of the neurochemical extracellular milieu may provide additional indices for early detection of vasospasm.

In some neurosurgical settings the activity of single neurons offers useful information. Single-unit recordings have been used in the identification of targets for stereotactic procedures in patients with Parkinson's disease, most notably the globus pallidus internus during pallidotomies[22,32,36] and the subthalamic nucleus in deep brain stimulation procedures.[18,21] At the same time there is growing evidence of the importance of interactions of various neuromodulators (mainly dopamine, glutamate, and GABA) in this disorder,[20] as well as the influence of lesions and deep brain stimulation on these modulators.[13] Coupling microdialysis with neurophysiological techniques in these patients provides a new approach to characterizing neuronal function in the parenchyma. For example, the pathologically high firing rate of glutamatergic neurons in the globus pallidus of patients with Parkinson's disease can be detected with single-unit recordings during pallidotomies.[17] Microdialysis in this setting offers the capability of measuring glutamatergic correlates of the electrophysiological observations.

A potentially important use of microdialysis in a clinical setting may be the introduction of substances into the parenchyma for manipulation of the extracellular environment. During, et al.,[7] demonstrated potassium-stimulated release of GABA in the human hippocampus and found that glutamate-induced calcium-independent release of GABA was markedly reduced in the epileptogenic hippocampus compared with the contralateral hippocampus. Such studies demonstrate the feasibility of changing the local extracellular environment, suggesting a route for local neurochemical intervention in neurological diseases. The microdialysis technique has several advantages as a method of drug delivery to the brain parenchyma. These include the capability of delivering drugs to a precise target while minimizing the introduction of a fluid load into the parenchyma, because the method of delivery is by diffusion along a concentration gradient.

In our experience the placement of the depth electrodes as described here produces a minimal risk of morbidity. Because the placement procedure includes multiple penetrations of the cortical surface, we believe that both angiographic and MR studies are necessary for surgical planning. Magnetic resonance angiography may be used in place of plain angiography, but we find that the cortical veins are better appreciated on DS angiography and therefore we have been reluctant to rely solely on the MR modality. No signs of infection have been encountered and care has been taken to prevent CSF leakage by using secured guide screws with caps fitted with O-rings to obtain an optimal seal.

Conclusions

Placement of multiple intracranial electrodes coupled with probes for microdialysis and single-unit recording can be safely accomplished, and concomitant measurement of EEG, single-neuron activity, and neuroactive substances in the extracellular milieu in specific brain targets can be performed at the bedside. Release of amino acids and biogenic amine neurotransmitters can be measured at 5- to 10-minute intervals during seizures and during cognitive activity. The technique described here can be applied to various neurosurgical settings such as in the evaluation of patients with head injury, epilepsy, and SAH or during procedures in which electrophysiological and neurochemical characterization of the specific brain targets is important.

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Disclosure

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