RSV IV (experiment 3 in Table 1). The latter phenomenon could be explained as competitive inhibition of the polyamine toward TG-catalyzed modification of RSV IV, since in that experimental situation TG should be able to link Spd to the sperm surface and modify RSV IV.

In conclusion, our findings suggest that the polyamines play a physiological role as fine regulators of RSV IV binding to sperm. The capacity of the native form of RSV IV to partially inhibit Spd binding to sperm allows the attractive speculation of a reciprocal interference of the two biochemical phenomena.

G. PAONESSA
S. METAFORA
Institute of Molecular Embryology, National Research Council, Naples, Italy
G. TAJANA
Institute of Normal Human Anatomy, Second Medical School, University of Naples, Naples, Italy
P. ABRESCIA
Institute of Organic and Biological Chemistry, Faculty of Science, University of Naples
A. DE SANTIS
V. GENTILE
R. PORTA*
Institute of Chemistry and Biological Chemistry, First Medical School, University of Naples

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* To whom correspondence should be addressed at Istituto di Chimica e Chimica Biologica, via Costantinopoli 16, 80138 Napoli, Italy.

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Fast and Slow Magnetic Phenomena in Focal Epileptic Seizures

Abstract. *The magnetic fields associated with penicillin-induced focal epilepsy were measured in laboratory rats. Interictal magnetic spikes were similar to those previously observed in humans with focal seizure disorders. The magnetic fields of the seizure itself displayed both slow and fast phenomena, reversing in direction on opposite sides of the head.*

The ionic currents associated with the production of electrically measurable epileptic seizures must also generate detectable extracranial magnetic fields in many circumstances. However, measurements of the magnetic fields produced by these localized paroxysmal electrical events have not been reported (*1*). Although magnetic and electrical phenomena are related, they nonetheless may reveal different information about current flow within underlying cortical structures. In contrast to the electric field, magnetic fields normal to the scalp are not distorted or attenuated by the resistive properties of the cranium (*2*). Furthermore, neuromagnetic fields are sensed without physical contact, facilitating the study of slow cortical activity (*3*), which is difficult to measure electrically because of problems at the electrode-tissue interface (*4*).

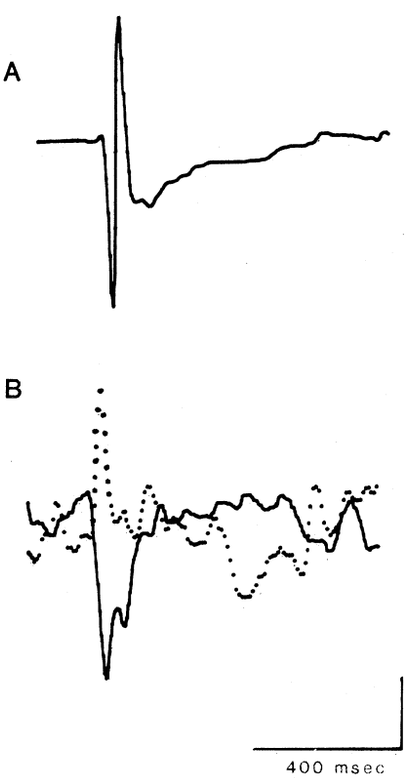

Fig. 1. Interictal activity of animal 1. (A) Averaged biphasic interictal spike in the ECoG (negative down). (B) Averaged interictal spikes in the MEG recorded from bilateral sites (solid and dotted traces) differ from the ECoG spike in morphology and are of opposite direction between sites, reflecting magnetic flux emerging from (upward) and reentering (downward) the cranium. Vertical calibration: MEG, 240 fT; ECoG, 500 μV.

We have previously reported that the electrical spikes in patients with focal epilepsy are accompanied by highly organized extracranial magnetic fields that we have mapped and used to locate probable intracranial current sources (*5*, *6*). These measures are made possible by a newly developed neuromagnetic sensing technique, the magnetoencephalogram (MEG). However, these brief interictal epileptic events occur between seizures and do not reflect the seizure discharge itself.

In order to obtain MEG measurements of the magnetic phenomena directly associated with seizure activity in focal epilepsy, we have used an animal model in which multiple seizures can be experimentally produced and verified with electrocorticography (ECoG). The injection of penicillin into the rat cerebral cortex produces stereotyped focal epileptic spiking and seizures in the ECoG. This animal model permitted us to repeatedly observe both fast and slow magnetic phenomena associated with focal epilepsy.

Four adult Sprague-Dawley rats (300 to 350 g) were studied. Fifteen minutes after the injection of atropine sulphate, general anesthesia (ketamine HCl, 100 mg/ml and xylazine, 20 mg/ml) was initiated and maintained. The animals were paralyzed with an interperitoneal injection (3 ml) of gallamine triethiodide (20 mg/ml) and artificially ventilated. A craniectomy was performed to expose a small region of the left hemisphere. Penicillin G potassium (4000 unit/μl) was injected into the cortex. Injections were made at two sites 2 and 4 mm caudal to bregma in the first rat and a single site 2 mm caudal to bregma in the remaining three rats, all at a depth of 1.75 mm and angle of 30°, 2 mm lateral to midline. This procedure created unilateral medial seizure foci that in unparalyzed animals produced reliable electrographic and behavioral focal seizures.

The ECoG was recorded with a solder-plated copper wire electrode placed directly on the dural surface overlying the injection sites and referred to the back of the neck. The electrocardiogram (EKG) was also monitored. The MEG was recorded with a single-channel second-de-

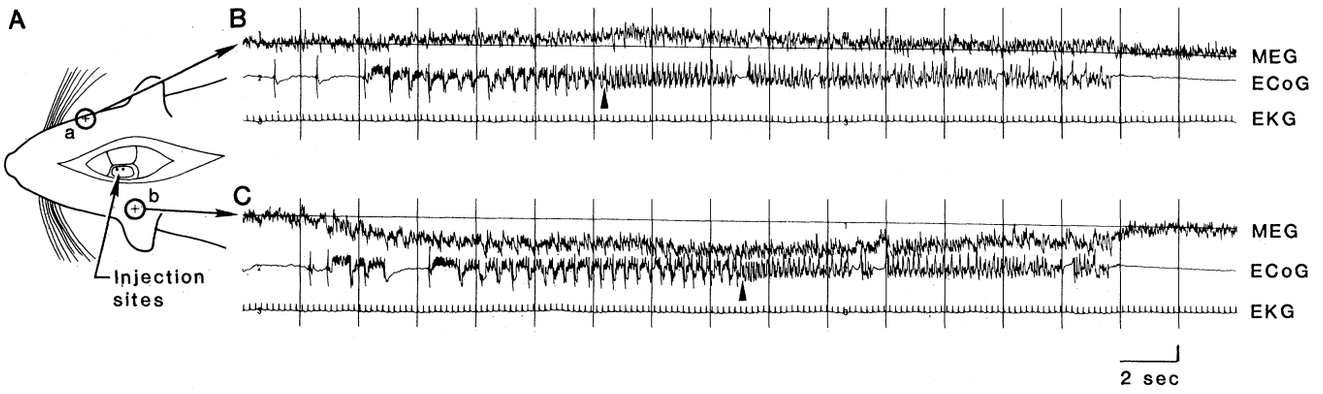

Fig. 2. Two separate seizures recorded from animal 1. (A) Left hemisphere craniectomy and penicillin injection sites (dots). (B and C) Sequential MEG recordings from sites a and b, respectively (top traces), of two separate focal seizures display field shifts of opposite direction with rapid spiking superimposed. Each seizure in the ECoG began with afterdischarge followed by rapid spiking (arrows) and terminated abruptly with postictal depression. Spikes in the MEG and ECoG are unrelated to EKG. The seizures depicted in (B) and (C) were not recorded simultaneously, but instead reflect sequential MEG measurement of two separate seizures. Vertical calibration: MEG, 480 fT; ECoG, 800 μV.

rivative superconducting gradiometer (*7*) sequentially positioned approximately normal to the skull over each of two sites on opposite sides of the head. At least three seizures were recorded separately at each of these MEG measurement sites. The ECoG, EKG, and MEG were amplified with a Grass model 8-18 C electroencephalograph (filtered with −3-dB attenuation at 1 to 70 Hz). The MEG was also amplified separately with a d-c-coupled amplifier (National Semiconductor LM356, low pass filtered with −3-dB attenuation at 100 Hz). All signals were plotted on a paper chart recorder as well as digitally sampled (256 Hz, 12 bits) and stored on magnetic tape for further analysis.

Seizure activity in the raw MEG and ECoG was directly observable in the chart recordings. Digitized seizure data were displayed on a storage cathode-ray tube and the peaks of the earliest 20 to 30 rapid spikes in the ECoG of each seizure were visually identified. These points were then used as time markers to compute averages of the MEG and ECoG spikes across successive seizures recorded with the single channel MEG probe positioned over a given point. Separate averages were computed similarly for interictal spikes. The procedure for averaging magnetic and electrical data to visually identified electrical spikes has been reported (*5, 6*).

Repetitive interictal spikes appeared in the raw ECoG from 1 to 15 minutes after the injection of penicillin. The averaged interictal spikes in the ECoG were typically biphasic and followed by a long slow wave (Fig. 1A). In all animals, the initial spike recorded in the averaged MEG from bilateral sites (dotted and solid traces in Fig. 1B) was similar to that of the ECoG, but later components differed in morphology. Such morphological variations also have been reported for simultaneous electrical and magnetic recordings of interictal spikes in humans (*6*). All temporal components of the MEG spike in these animals reversed direction between the two MEG recording sites, reflecting magnetic flux emerging from (upward) and reentering (downward) the cranium.

For 1 to 2 hours after the injection of penicillin, afterdischarges (*8*) accompanied interictal spiking in the ECoG and culminated in spontaneous seizures recurring every 5 to 10 minutes. Seizure onset was characterized in the ECoG by an increase in interictal spike frequency and the appearance of afterdischarges after each spike (middle trace, Fig. 2, B and C). The period of afterdischarge was followed by rapid spiking (arrow), which decreased in frequency and increased in amplitude over the duration of the seizure (20 to 180 seconds). Spiking terminated abruptly at the end of the seizure and was followed by a period of depressed activity in the focus.

The most apparent response in the MEG to focal seizures in all animals was a steady magnetic field shift from preseizure baseline (top traces in Fig. 2, B and C). Three features of the shift were common among all four animals: the steady field shift began at the appearance of afterdischarge, reached a maximum at the onset of rapid seizure spiking, and dropped abruptly to baseline at the end of the seizure. In two animals with longer ictal episodes (2 to 3 minutes), the end of ictus was marked by a series of short seizure bursts. Each of these was accompanied by a large corresponding magnetic field shift, rising and falling abruptly with the onset and termination of each burst. Although the time course and amplitude of the shift in the MEG varied from animal to animal, these features were stable for each animal over successive seizures measured at a given extracranial point. The polarity of the magnetic field shifts were consistent across all animals, indicating magnetic flux emerging from the right side of the cranium and reentering on the left (a and b in Fig. 2A).

Fast seizure spiking was apparent also in the raw MEG, although smaller in amplitude than the slow magnetic field shifts. Fast activity was best visualized after averaging. The time locking points for seizure spikes were located in the midpoint of the 1-second averaging window, resulting in an averaged spike in the center of the trace in both the ECoG (Fig. 3A) and MEG recorded from the bilateral sites (Fig. 3B). These spikes were surrounded by smaller deflections at the approximate period of the repetitive discharge. This fast magnetic seizure activity also reversed direction between the two MEG recording sites.

These data indicate that large extracranial fields are produced by focal penicillin seizures in the rat. In all seizures studied neuromagnetically, the most prominent signal in the MEG was a steady magnetic field shift lasting the duration of the seizure. These slow magnetic phenomena are similar to d-c electrical shifts recorded from the penicillin focus with nonpolarizable electrodes (*9, 10*). The d-c electrical changes are believed to be an electrophysiological characteristic of epileptic seizures in general (*10*), but have not been widely studied, in large part because of technical difficulties associated with d-c electrical recording. A number of factors may explain

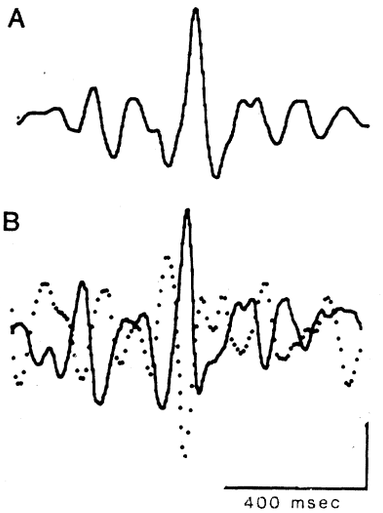

Fig. 3. Fast seizure spiking in animal 1. (A) Averaged rapid seizure spike in the ECoG (negative down). (B) Seizure spikes averaged across three successive seizures recorded in the MEG at each of the bilateral sites (solid and dotted traces) are similar in morphology to the ECoG and are of opposite direction between recording sites. (Emerging and reentering fields are shown by upward and downward traces, respectively.) Vertical calibration is the same as in Fig. 1.

why slow shifts are less difficult to record magnetically; of particular importance is the absence of a tissue-electrode interface and the inherently wide frequency response of superconducting magnetometers (d-c to 10 kHz).

Our data provide measurements of both the fast and slow magnetic phenomena associated with focal electrographic seizures. These phenomena indicate strong electric currents occurring at the cellular level within the epileptic focus. In all animals, the magnetic fields associated with both interictal and ictal activity were consistently reversed in direction between the two MEG recording sites, indicating an organized pattern of emerging and reentering magnetic flux. Although these recordings were performed with a single channel MEG sensor, the repeatability of ictal and interictal magnetic phenomena at a given MEG recording site permitted comparison between separate epileptiform events sequentially recorded at each of the bilateral locations.

This experiment also represents a use of an animal model for the neuromagnetic study of central nervous system events. Although accomplished with a large-coil instrument designed for the study of the human brain, neuromagnetic phenomena produced in much smaller brains like that of the rat may be measured if proper attention is paid to the diameter and separation of the gradiometer coils in relation to the measurement distance (*11*).

The magnetic phenomena observed here in laboratory animals with experimentally induced epileptic foci may also be of practical consequence. The slow field shifts associated with the development of seizures are very strong. For this reason, slow field shifts should be suited for neuromagnetic mapping in patients with focal seizure disorders. Although electrical measurements of slow focal seizure phenomena in humans has been performed during neurosurgery (*12*), noninvasive electrical mapping of these major slow events has not been possible to our knowledge. Neuromagnetic sensing therefore may be a useful method for noninvasively localizing the seizure focus in human beings with focal epileptic disorders.

DANIEL S. BARTH
Departments of Psychology and *Neurology, University of California, Los Angeles 90024*
WILLIAM SUTHERLING
Department of Neurology, University of California, Los Angeles
JACKSON BEATTY
Department of Psychology, University of California, Los Angeles

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Benzodiazepine Receptor Synthesis and Degradation by Neurons in Culture

Abstract. *The benzodiazepine–γ-aminobutyric acid receptor complex was used to study functional receptor synthesis and degradation in primary cultures of neurons. Fifty percent of the receptors turned over with an unusually rapid half-life (4 hours); this was followed by a second, slower phase (32 hours). These results provide the basis for elucidating the mechanism by which neurons derived from the central nervous system control neurotransmitter receptor number, an important problem in cellular neurobiology. The findings may be of significance in the study of neurological and psychiatric disorders.*

Synaptic transmission at chemical synapses involves a well-described sequence of events in which a neurotransmitter is released from the presynaptic terminal and interacts with postsynaptic receptors that transduce ligand binding into a postsynaptic response. One way a neuron can regulate its sensitivity to a ligand is by altering the number of postsynaptic receptors. The mechanism by which receptor numbers are controlled is thus of central importance in neurobiology. Receptor numbers under steady-state conditions are ultimately controlled by the relative rates of receptor synthesis and degradation, and an understanding of such rates should help to elucidate the mechanism of receptor regulation. Except for the nicotinic cholinergic receptor in skeletal muscle (*1*), little is known about the turnover of neurotransmitter receptors (*1*). This is due, in part, to the complexity and relative inaccessibility of the central nervous system (CNS) and to the lack of specific, irreversible probes. Neurotransmitter receptor turnover kinetics have typically been inferred from the rate of cycloheximide-induced receptor loss (*2*) or from agonist-induced decreases in receptor number (down-regulation) (*3*). However, cycloheximide is now known to alter receptor degradation (*4*), and down-regulation may involve mechanisms distinct from