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Endocrine Abnormalities in Human Temporal Lobe Epilepsy

BRIAN B. GALLAGHER, M.D., Ph.D.

Department of Neurology, Medical College of Georgia, Augusta, Georgia

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Patients with temporal lobe epilepsy secrete ACTH at higher rates and in greater amounts than normal subjects. Temporal lobectomy restores ACTH secretion to normal amounts and rates. The ACTH secretion in temporal lobe epilepsy is independent of anticonvulsant drug effect and seizure frequency. Electrical stimulation of medial temporal lobe structures in patients with temporal lobe epilepsy affected ACTH secretion in a manner consistent with the hypothesis that ACTH secretion is regulated by tonic inhibition. A defect in the excitatory and/or inhibitory components of this regulatory process appears to exist in temporal lobe epilepsy.

Hypercortisolemia in temporal lobe epilepsy has been reported [1]. This article will review our investigations of this observation. We have studied ACTH and other pituitary hormone secretion in patients with temporal lobe epilepsy, pseudoseizures, and normal controls. We have also examined the effect of electrical stimulation of medial temporal structures upon secretion of these hormones. Our findings are consistent with the hypothesis that ACTH secretion is, in part, regulated by tonic inhibition from medial temporal lobe structures and this inhibition is perturbed in temporal lobe epilepsy.

The basic procedure for studying hormone secretion was constant for each study. With the subject comfortably lying in bed, an indwelling venous catheter was placed in an arm vein. Blood samples were collected atraumatically every five minutes for the duration of the study. Details of the procedure and the hormone radioimmunoassays have been described [3]. The data calculated included mean hormone concentration during the collection period and secretory rate when secretion occurred [4].

Patients with depth electrodes implanted bilaterally in amygdala and hippocampus were studied during electrical stimulation of these structures, which was conducted to determine threshold for after-discharge and to elicit the patient's typical seizure or seizure onset. A two-channel stimulator (Grass Instruments Co., Quincy, MA) with isolation and current control circuits provided balanced square-wave stimuli of 60 Hz, 150 V, 2 Ms, and 0.05 to 5 mA. A three-second train of stimuli was passed between contact points separated by 10 mm with a recording contact between. Stimulus trains were applied once per minute, starting at 0.05 mA, with each stimulus train increasing by 0.05 mA to 0.5 mA, and at 0.1 mA increments thereafter until an after-discharge occurred. If the after-discharge was longer than ten seconds in duration or a seizure occurred, stimulation was suspended for 30 minutes while blood collection continued.

PROTOCOL 1

ACTH secretion was determined in patients with temporal lobe epilepsy and patients with pseudoseizures who were receiving anticonvulsant drug treatment and who were known not to have epilepsy (Table 1).

Address reprint requests to: Brian B. Gallagher, M.D., Ph.D., Dept. of Neurology, Medical College of Georgia, Augusta, GA 30912

TABLE 1
ACTH Determined Every Five Minutes Between 0800–0930 Hours [2]

Group (N)	ACTH	
	$\bar{x}$ Concentration ± SD (pg/ml)	$\bar{x}$ Secretory Rate ± SD (μg/minute)
Epilepsy (5)	91 ± 38	0.72 ± 0.21
Pseudoseizures (5)	62 ± 34[a]	0.38 ± 0.11[a]

[a] $p < 0.05$ (t-test)

TABLE 2
ACTH Secretion in Normal Controls, Pre-Operative Patients, and Post-Operative Patients with Temporal Lobe Epilepsy
(Blood sampled every five minutes between 1400 and 1600 hours [2].)

Group (N)	ACTH	
	$\bar{x}$ Concentration ± SD (pg/ml)	$\bar{x}$ Secretion Rate ± SD (μg/minute)
Normal (9)	38.1 ± 12.9	0.327 ± 0.102
Temporal lobe epilepsy (7)	110 ± 65[a,b]	1.07 ± 0.7[a,b]
Post-Operative (11)	30.1 ± 15.1	0.334 ± 0.195

[a] Temporal lobe epilepsy greater than normal, $p < 0.001$
[b] Temporal lobe epilepsy greater than post-operative, $p < 0.01$ (t-test)

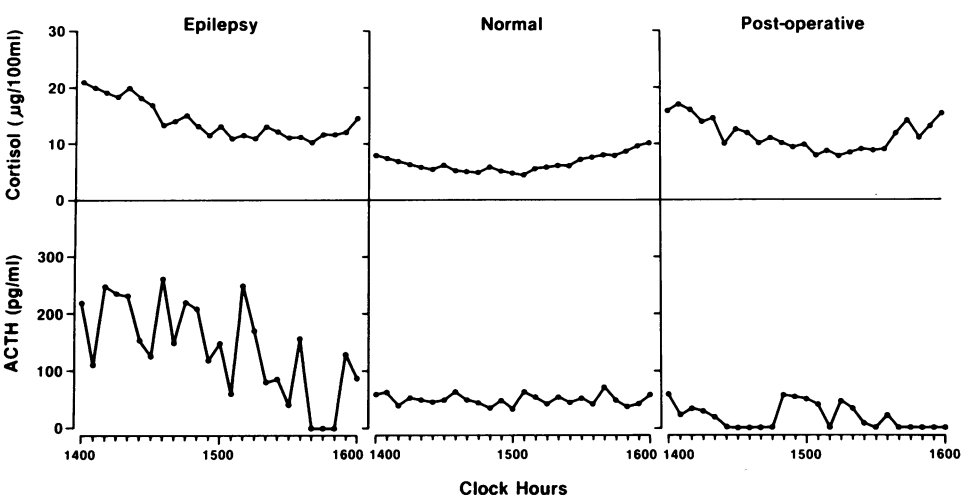

FIG. 1. ACTH and cortisol measured simultaneously every five minutes in three typical subjects [2].

TABLE 3
ACTH Secretion During Electrical Stimulation of Medial Temporal Lobe Structures (1400–1600 hours [3])

	ACTH	
Study Type (*N*)	$\bar{x}$ Concentration ± SD (pg/ml)	$\bar{x}$ Secretory Rate ± SD (μg/minute)
Negative (7)	4.27 ± 4.1	0.50 ± 0.36
Positive (3)	182.7 ± 52.6[a]	1.33 ± 0.97[a]

[a]Significantly different, $p < 0.001$ (t-test)

PROTOCOL 2

ACTH and cortisol were determined in normal controls, temporal lobe epilepsy patients, and post-operative temporal lobectomy patients. Blood was sampled between 1400 and 1600 hours [2]. ACTH was significantly elevated in the temporal lobe epilepsy patients in comparison to the other two groups (Table 2) whether or not seizure control was attained. The obvious difference in ACTH between the temporal lobe epilepsy patients and the other two groups is illustrated in Fig. 1.

PROTOCOL 3

ACTH, prolactin, and growth hormone were measured during electrical stimulation of amygdala or hippocampus in patients with temporal lobe epilepsy undergoing pre-surgical evaluation for temporal lobectomy [3]. Stimuli applied to either structure, ipsilateral or contralateral, to the seizure focus appeared to inhibit ACTH secretion but had no effect upon prolactin secretion, if an after-discharge did not occur or did not exceed ten seconds in duration. These were termed "negative" studies (Table 3 and Fig. 2). When either multiple after-discharges longer than ten seconds in duration or a

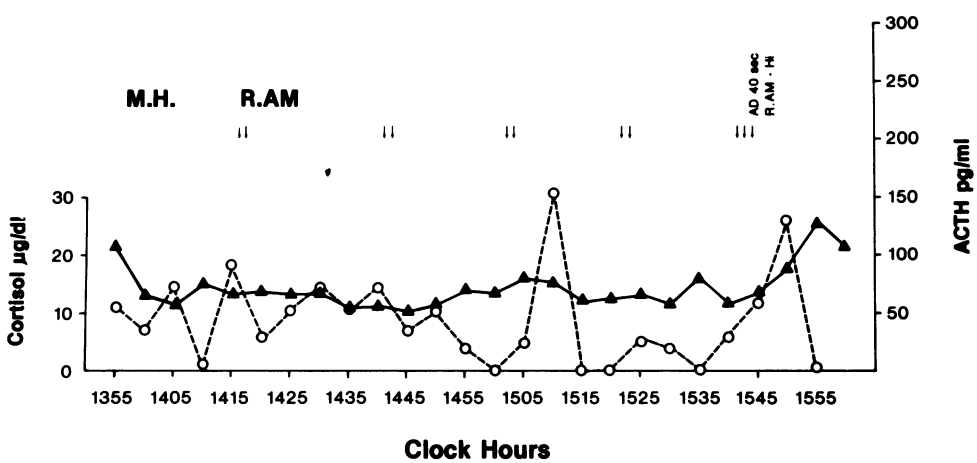

FIG. 2. Typical example of a negative stimulation study. The after-discharge (AD) occurring at the end of the study was excluded from the calculations. Arrows indicate application of stimulus trains (balanced square waves, 60 Hz, 150 V, 2 Ms, 0.05 to 5 mA; three-second trains). O-----O ACTH; ▲—▲ cortisol [3].

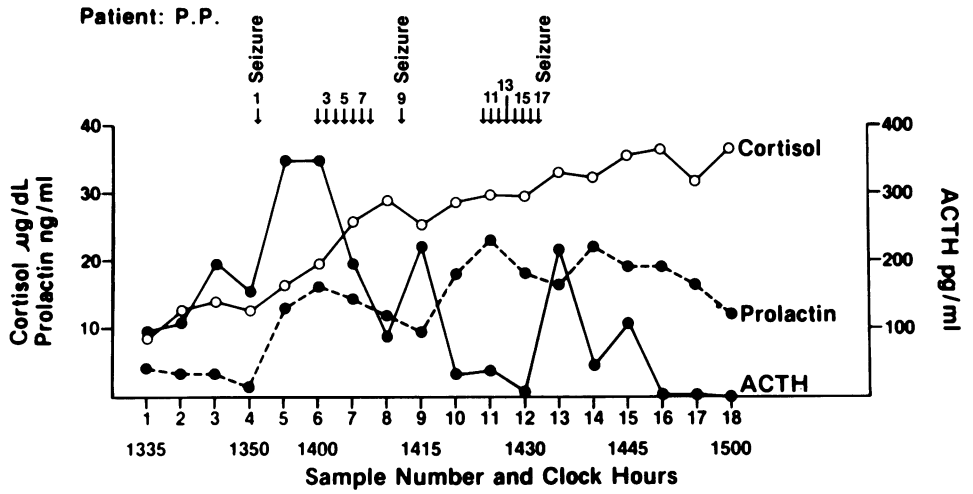

FIG. 3. Typical example of a positive stimulation study [3].

seizure occurred, these were called "positive" studies (Fig. 3). Studies consisting of a mixture of positive and negative events were too difficult to analyze (Fig. 4).

In contrast to the negative studies, which had no apparent effect upon prolactin secretion, prolonged after-discharges or seizures also resulted in prolactin secretion but had no effect upon growth hormone (Table 4).

DISCUSSION

The abnormal secretion of ACTH in patients with temporal lobe epilepsy is related to the epileptic abnormality in the medial temporal lobe because secretion returns to normal following temporal lobectomy. It is independent of drug effect because it was

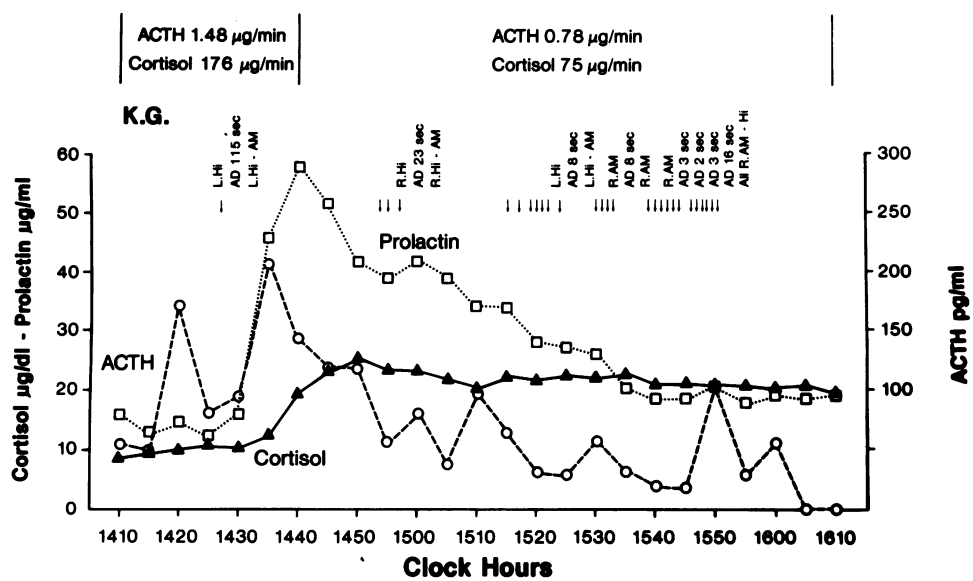

FIG. 4. Typical example of a mixed study. Note the difference in secretory rates associated with the seizure [3].

TABLE 4
Comparison of ACTH Secretion in Patients with Electrographic After-Discharges (AD) and Patients with Clinical Seizures During Electrical Stimulation of Medial Temporal Lobe Structures [3]

	AD	Seizures
	ACTH	
N	6	7
$\bar{x}$ Duration of AD (seconds)	69 ± 37	N/A
$\bar{x}$ Concentration (pg/ml)	85 ± 37	294 ± 154
$\bar{x}$ Rate (μg/minute)	0.73 ± 0.5	2.17 ± 1.1
	Prolactin	
N	4	4
$\bar{x}$ Concentration (ng/ml)	+37 ± 8	+51 ± 40
	Growth Hormone	
N	2	N/A
$\bar{x}$ Concentration (ng/ml)	0	—

not found in the patients with pseudoseizures who were receiving anticonvulsant drugs. It is also independent of seizures because ACTH secretion became normal following temporal lobectomy, whether or not seizures were controlled by the operation. It appears to be specific for ACTH, at least in comparison to prolactin and growth hormone.

Multiple transmitter systems appear to be involved in the control of most of the hormones secreted by the pituitary [5]. For ACTH, acetylcholine is stimulatory and glucocorticoids are somehow involved in an inhibitory role. Our studies of electrical stimulation of medial temporal lobe structures are admittedly difficult to interpret, as are any stimulation studies in the central nervous system. Nevertheless, the ultimate effect of the electrical stimulation upon ACTH is clear. Stimuli that do not activate after-discharge longer than ten seconds in duration inhibit ACTH secretion, while longer after-discharges and seizures produce secretion of ACTH and prolactin but not growth hormone. We interpret these observations to be consistent with the hypothesis that ACTH secretion is under tonic inhibitory control by medial temporal lobe structures. We speculate that the abnormal ACTH secretion is a result of a deficit in the glucocorticoid-mediated inhibition of ACTH secretion and a relative hypercholinergic state in the medial temporal lobe structures of patients with temporal lobe epilepsy. The biological consequences of chronic exposure to high ACTH and cortisol secretion are not clear at the present time. The absence of stigmata of hypercortisolemia and the preservation of the normal 24-hour pattern of cortisol secretion in temporal lobe epilepsy patients are observations deserving further study.

REFERENCES

1. Gallagher B: Adrenal hyperplasia in epileptic patients. In Quantitative Analytical Studies in Epilepsy. Edited by P Kellaway, I Petersen. New York, Raven Press, 1976, pp 165–169
2. Gallagher B, Flanigin H, King D, et al: Pituitary and adrenal function in epileptic patients. Epilepsia 25:683–689, 1984
3. Gallagher B, Flanigin H, King D, et al: The effect of electrical stimulation of medial temporal lobe structures, in epileptic patients, upon ACTH, prolactin, and growth hormone. Neurology, in press
4. Gallagher T, Yoshida K, Roffworg H, et al: ACTH and cortisol secretory patterns in man. J Clin Endocrinol Metab 36:1058–1068, 1973
5. Tuomisto J, Mannisto P, et al: Neurotransmitter regulation of anterior pituitary hormones. Pharmocal Rev 37:249–332, 1985