1977

Elevation of seizure thresholds by cerebellar stimulation

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Elevation of seizure thresholds by cerebellar stimulation

by

George Michael Strain

A Dissertation Submitted to the

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Biomedical Engineering
Co-majors: Physiology
Biomedical Engineering

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For the Graduate College

Iowa State University
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1977

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INTRODUCTION

Seizures, physiological events in which voluntary control of motor activity and mentation are lost, are caused by a massive electrical discharge of large aggregates of neurons. The discharge may remain localized or spread to become generalized and include major portions of the brain. Associated with these discharges may be tonic and/or clonic convulsions, loss of consciousness, or both, as well as manifestations of the brain regions involved, evoking sensory, motor, autonomic, or ideational symptoms.

Although seizures may be caused by transient attacks of cerebral ischemia, withdrawal from drug addiction, or febrile episodes in early childhood, most are due to the numerous disease states collectively referred to as epilepsy. Among the etiological classifications of epilepsy employed by the National Institute of Neurological Diseases and Blindness (Robb, 1965) are genetic and birth factors, infections, toxins, traumas, metabolic disturbances, and neoplasms. However, the etiology of a specific case of epilepsy is frequently unknown.

If a cure for the seizures, such as correction of a metabolic disturbance or excision of pathological tissues, is not possible, seizure control is attempted with drug therapy. Of the estimated four million epileptics in the United States, about half achieve complete control of their seizures with anticonvulsant drug therapy, and thirty percent achieve partial control (Epilepsy Foundation of America, 1975). The remaining 800,000 epileptics are uncontrolled, and as a result may be severely handicapped. A recent approach to the control of seizures is

electrical stimulation of the cerebellar cortex. Although anticonvulsant drug therapy is well-established, cerebellar stimulation as a means of seizure control is unproven; preliminary reports and clinical investigations have provided equivocal results. In particular, optimum stimulation parameters are as yet uncertain, and the effectiveness of stimulation therapy in comparison with current therapies is uncertain.

In the present research, models of generalized seizure states are evoked by intravenous pentylenetetrazol and electrical stimulation of the frontal cerebral cortex. Comparisons are made of the anticonvulsant efficacy of cerebellar stimulation, phenobarbital and diphenylhydantoin in acute, conscious New Zealand albino rabbits. Specifically, cerebellar stimulation parameters are determined that are effective in reducing seizure activity in these preparations. The elevation of EEG seizure thresholds by cerebellar stimulation and anticonvulsant drugs is analyzed and an assessment of the efficacy of cerebellar stimulation in comparison with phenobarbital and diphenylhydantoin is made.

LITERATURE REVIEW

Anatomy and Physiology

The cerebellum (Figure 1) traditionally has been considered to function in the coordination of muscle movements. However, current research has shown that it is involved in neural activity in a much larger scope, to include the monitoring of activity of spinal inhibitory interneurons and modulation of sensory neural input (Llinas, 1975; Wolfe and Kos, 1975).

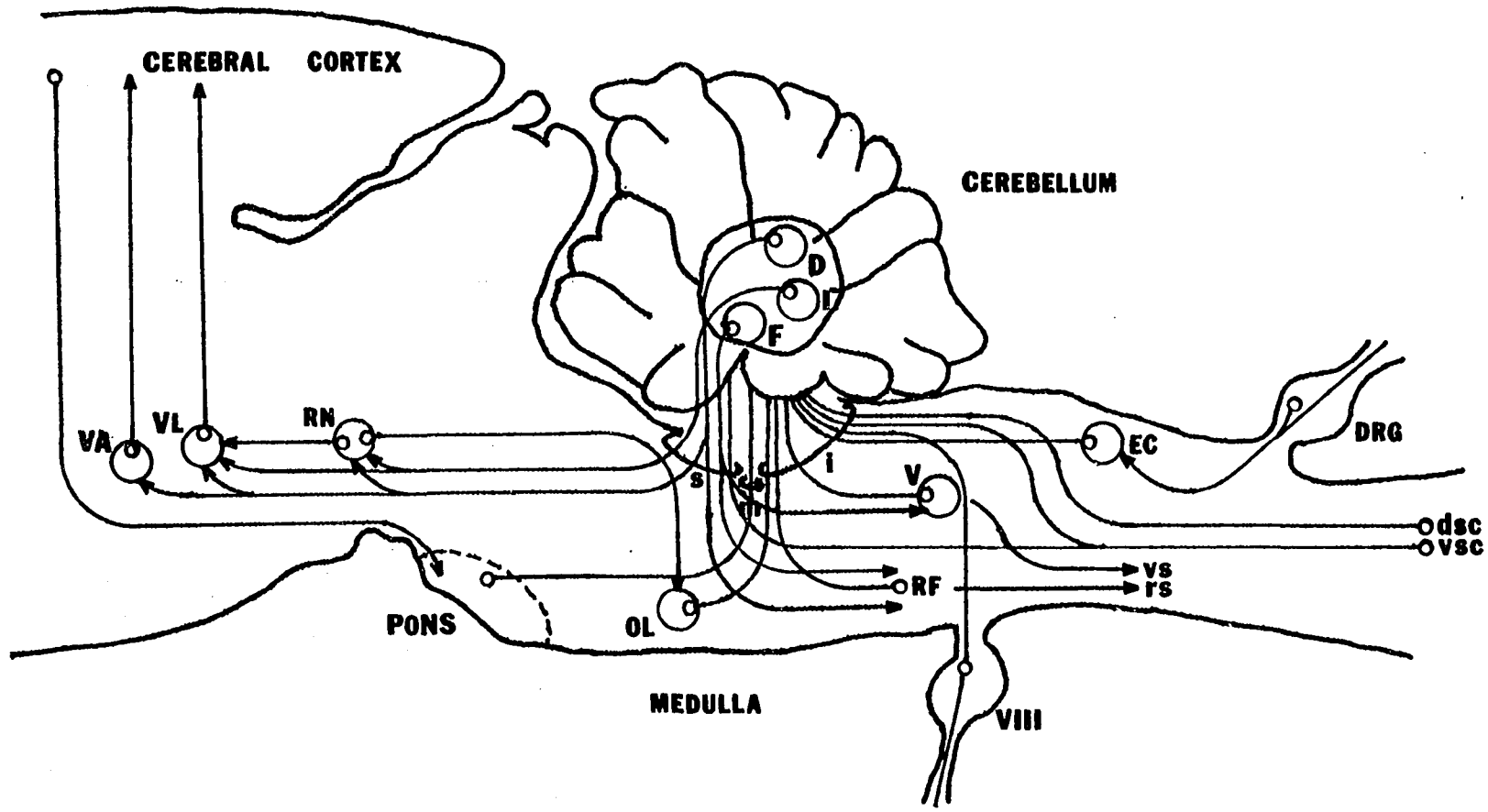
The cerebellum can be divided into two major sections: an outer cortex, and a central region of white matter which includes several pairs of aggregates of nerve cells known as the cerebellar nuclei. Afferents to and efferents from the cerebellum pass through the cerebellar peduncles (superior, middle, and inferior), the connections between the cerebellum and the brain stem. Afferent and efferent fiber tracts and their origins or terminations are presented in Table 1. The efferent fibers are the axons of the cells of the cerebellar nuclei, or the axons of the few Purkinje cells which project directly to the vestibular nucleus.

The cerebellar cortex is divided phylogenetically into two major divisions (Figure 2): the older paleocerebellum, consisting of the medially located anterior lobe, the paraflocculus, uvula, and pyramis (which receive vestibular afferents), and the flocculus and nodulus (which receive spinal afferents); and the newer neocerebellum, present only in warm-blooded animals, consisting of the posterior lobes, which

Figure 1. Cerebellar connections with other central nervous system structures (redrawn from Palay and Chan-Palay, 1974).

Key:

D	dentate nucleus
DRG	dorsal root ganglion
dsc	dorsal spinocerebellar
EC	external cuneate nucleus
F	fastigial nucleus
I	interpositus nucleus
i	inferior cerebellar peduncle
m	middle cerebellar peduncle
OL	olivary nucleus
RF	reticular formation
RN	red nucleus
rs	reticulospinal tract
s	superior cerebellar peduncle
V	vestibular nucleus
VA	ventroanterior nucleus of the thalamus
VIII	eighth cranial nerve ganglion
VL	ventrolateral nucleus of the thalamus
vs	vestibulospinal tract
vsc	ventral spinocerebellar tract


CEREBRAL CORTEX
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MEDULLA
VIII

Table 1. Afferent and efferent tracts of the cerebellum

Afferents	
Tract	**Origin**
dorsal spinocerebellar	spinal cord
rostral spinocerebellar	spinal cord
ventral spinocerebellar	spinal cord
cuneatocerebellar	cuneate nucleus
vestibulocerebellar	vestibular nucleus
reticulocerebellar	reticular formation
olivocerebellar	olivary nucleus
pontocerebellar	pontine gray
pontobulbarcerebellar	pons and medulla
trigeminocerebellar	trigeminal nucleus
tectocerebellar	tectum
rubrocerebellar	red nucleus
Efferents	
Tract	**Termination**
cerebellovestibular	vestibular nucleus
cerebelloreticular	reticular formation
cerebellorubral	red nucleus
cerebellothalamic	thalamus
cerebellopallidal	globus pallidus
cerebellonuclear	nuclei of cranial nerves 3, 5, 6, 7

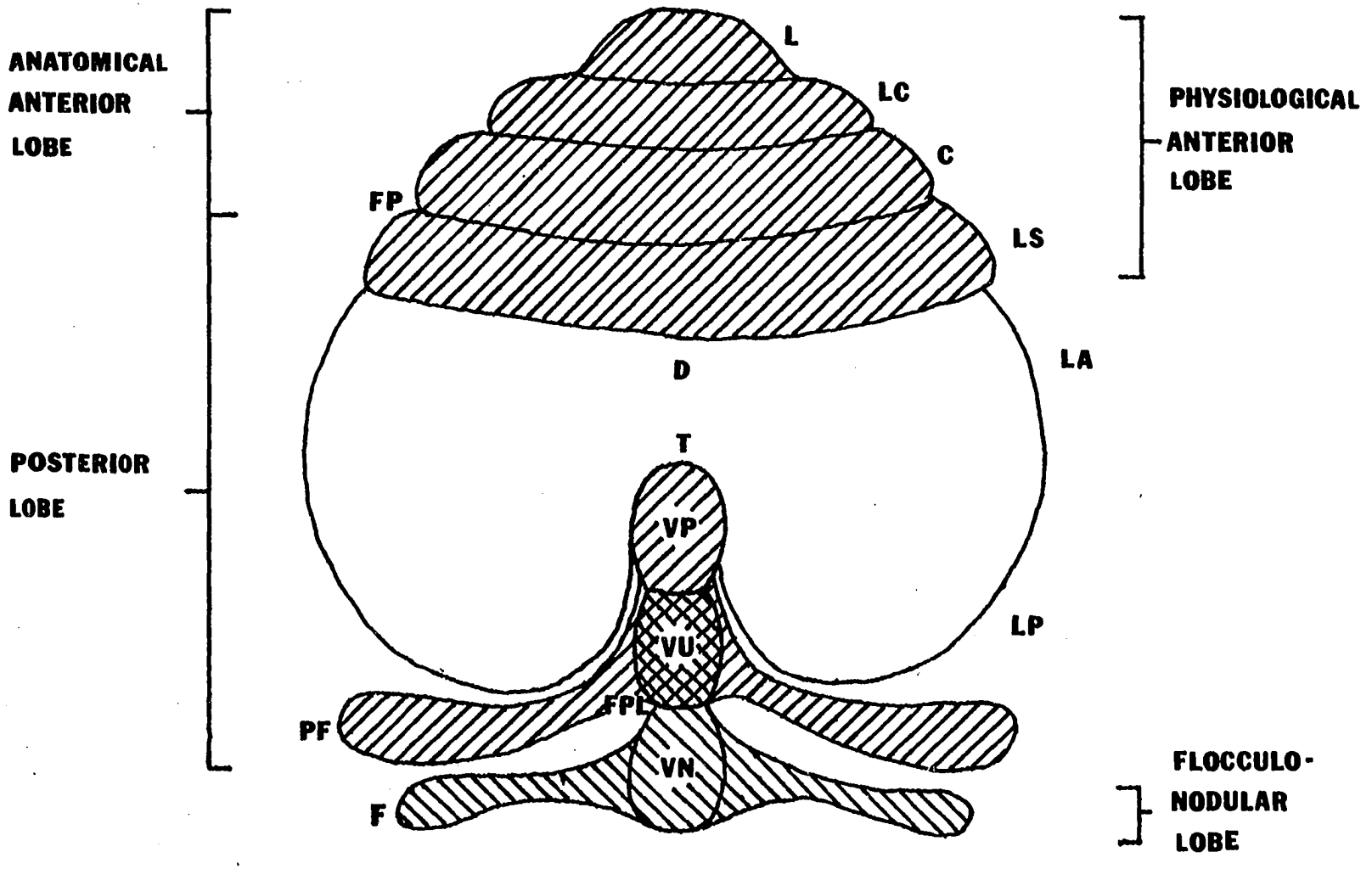
extend laterally as the cerebellar hemispheres. Afferents to the neocerebellum are the corticopontocerebellar fibers.

On a cellular level (Figure 3), the cortex consists of three concentric layers: molecular (outer), Purkinje (middle), and granular (inner). These layers are comprised of seven neural elements (five cell and two fiber types) arranged throughout the cortex in a precise, regular pattern (Llinas, 1975). Two elements, the climbing fibers and the mossy fibers, have previously been thought to provide the only input to the

Figure 2. Diagram of cerebellar cortex to show principal divisions (redrawn from Fulton, 1955, after Dow, 1942).

Key:

C	culmen
D	declive
F	flocculus
FP	fissura prima
FPL	fissura posterolateralis
L	lingula
LA	lobulus ansiformis
LC	lobulus centralis
LP	lobulus paramedianus
LS	lobulus simplex
PF	paraflocculus
T	tuber
VN	vermis - nodulus
VP	vermis - pyramis
VU	vermis - uvula


ANATOMICAL
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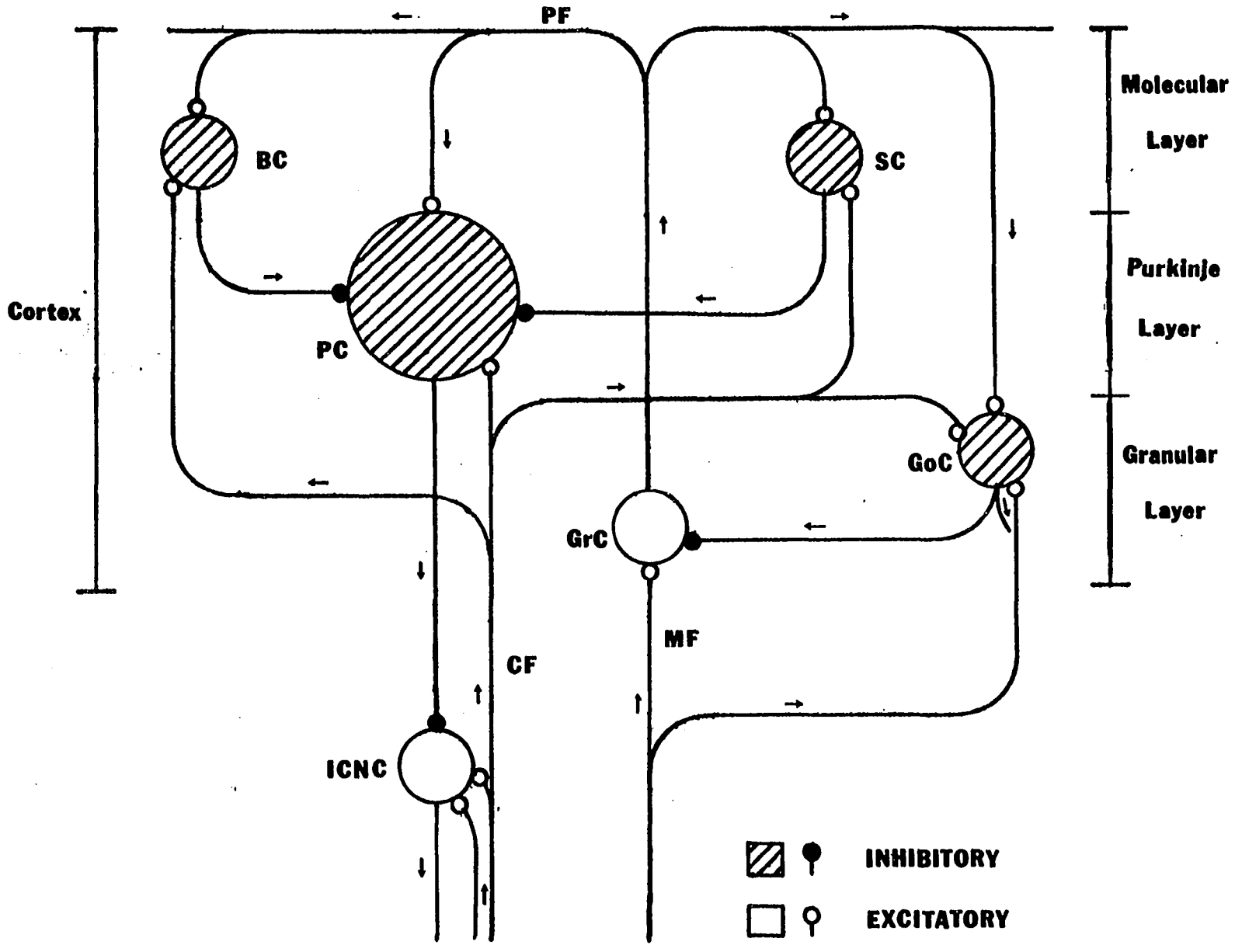
PF
VN
F
PHYSIOLOGICAL
ANTERIOR
LOBE
FLOCCULO-
NODULAR
LOBE
AFFERENT FIBER
CONNECTIONS:
CORTICOPONTOCEREBELLAR
VESTIBULAR
SPINAL
NEOCEREBELLUM
PALEOCEREBELLUM

Figure 3. Functional relationships among the cells and fibers of the cerebellum.

Key:

BC	basket cell
CF	climbing fiber
GoC	Golgi cell
GrC	granule cell
ICNC	intercerebellar nuclei cell
MF	mossy fiber
PC	Purkinje cell
PF	parallel fiber
SC	stellate cell


PF
Molecular
Layer
Purkinje
Layer
Granular
Layer
Cortex
BC
SC
PC
GoC
GrC
MF
CF
ICNC
INHIBITORY
EXCITATORY

cortex. However, projections from cerebellar nuclei to the cerebellar cortex have recently been reported (Tolbert et al., 1976). These fibers are the axons in the afferent tracts listed in Table 1. The axons of a third element, the Purkinje cell, provide the only output from the cortex. The remaining elements are also neurons: stellate and basket cells located in the molecular layer, and granule and Golgi cells located in the granular layer.

The input fibers make excitatory synaptic contacts with both cerebellar nuclei cells and cortical cells, while the output fibers make inhibitory synaptic contacts with their targets, the cells of the cerebellar nuclei and the vestibular nucleus of the brainstem. A mossy fiber input to the cerebellar cortex excites granule cells, the only excitatory cells within the cortex. Collaterals also excite Golgi cells, whose inhibitory outputs turn off the granule cells (feed forward inhibition). The axon of a granule cell, which becomes a parallel fiber, excites a Purkinje cell, resulting in an increase in the rate of impulses from the Purkinje cell axon (see below) to cells within the cerebellar nuclei. The parallel fiber also excites basket and stellate cells, whose inhibitory synapses shut off or decrease the firing rate of the Purkinje cell. Thus, a mossy fiber input ultimately results in a very short-term increase of inhibitory impulses from a Purkinje cell. Climbing fiber inputs directly excite Purkinje cells, again resulting in short-term increases in inhibitory impulses leaving the cortex. Since the stellate and basket cells may have synaptic contacts with many Purkinje cells, an excitatory input to one Purkinje cell results in a zone of inhibited Purkinje cells around it.

Within the cortex there are approximately 3×10^{10} granule cells, 3×10^{7} Purkinje cells, and 2×10^{8} stellate and basket cells (Eccles, 1973). Each mossy fiber excites about 400 granule cells, and each Purkinje cell receives approximately 80,000 parallel fiber synapses from the granule cell axons. Only one climbing fiber influences a given Purkinje cell; however, it makes a massive number of synaptic contacts on the cell membrane.

The electrical activity described above is superimposed on tonic firing of all cells within the cerebellar cortex; Purkinje cells in particular have a regular, rhythmic discharge rate of 20 to 50/sec (Eccles, 1967). Therefore, input patterns to the cortex produce relative increases or decreases in Purkinje firing rates, rather than bursts superimposed on an electrical silence.

Fibers leaving the cerebellar nuclei (thought to be primarily excitatory) project to both higher and lower centers (Figure 1), often forming feedback loops to the cerebellar cortex. Fibers to these higher centers can ascend to even higher centers or descend to lower centers, so that paths from one site to another may be complicated and redundant. Cerebellar efferents travel to the thalamus, red nucleus, vestibular nucleus, and reticular formation, and from these sites to the cerebral cortex, either directly or indirectly. Since the output of the cerebellar cortex is entirely inhibitory, it is thought that the cerebellum regulates neural activity by selective inhibition of on-going activity. However, since a decrease in tonic inhibition can functionally result in a net excitatory effect, this simplified view of cerebellar function may not be justified. The role that the inhibitory action of Purkinje cells plays in

the arrest or suppression of seizures by electrical stimulation of the surface of the cerebellum (or by naturally occurring processes), and the paths by which the effect is accomplished are not presently known. This ignorance of the mechanisms has not precluded the incorporation of cerebellar stimulation as a therapeutic adjunct in the control of the epilepsies and other movement disorders (Cooper, 1973); however, knowledge of such mechanisms would greatly influence the utilization of cerebellar stimulation in a clinical setting. Several proposed mechanisms will be discussed below.

Cerebellar Stimulation

Early investigations

If the brain is severed just anterior to the pons, the body goes into a state of spastic muscular contraction known as decerebrate rigidity. This response has been reported in cats, dogs, primates and humans (Dow and Moruzzi, 1958). Sherrington (1897) and Lowenthal and Horsley (1897) independently reported that electrical stimulation of the paleocerebellum (anterior cerebellum) of dogs or cats could inhibit the extensor hypertonus of decerebrate rigidity, particularly with ipsilateral stimulation. Lowenthal and Horsley found the same effect when stimulating the underlying white matter and the cerebellar peduncles. These reports were the first proof of the inhibitory function of the cerebellum, and are particularly important because they established that the effective stimulus site for the inhibition was localized on a specific portion of the cerebellar cortex.

In the ensuing fifty years, numerous investigations probed the mechanisms of the inhibitory effect and attempted to delineate the effective stimulus sites, but with little success (see Dow and Moruzzi, 1958, for an extensive review). Induction coils were employed for stimulation in most of the experiments performed up to the middle of the twentieth century. Since only brief "faradic shocks" could be produced, an increased response was obtained by an increase in stimulus voltage, resulting in a rapid deterioration of the animal preparation. In addition, stimulus rates (40-60 Hz) were kept constant and voltages were not measured. In spite of these criticisms, several important features were established. Weed (1914) reported that the inhibitory area in cats was limited to the superior vermis, while Cobb et al. (1917) achieved best results from the hemispheral portion of the anterior lobe. However, they suggested that this might have been due to current spread to the superior cerebellar peduncle. Miller and Banting (1922) found the entire anterior lobe and part of crus I (ansiform lobe) to be effective sites for inhibition. Bremer (1922) demonstrated that the inhibitory effect originated within the cerebellar areas stimulated, and that both forelimb and hindlimb rigidity were inhibited by stimulation of the same vermal location, ruling out somatotopic organization of the effect. Further experiments (Bremer, 1925) showed the effect to differ from spinal inhibition, where subtetanizing doses of strychnine eliminate the inhibitory effect and release the normally masked excitatory component of the ipsilateral flexor reflex. The areas found most effective were the anterior lobe and the pyramis. Denny-Brown et al. (1929) reported that stimulation at the

vermal-hemispheral border of the anterior lobe inhibited decerebrate regidity, the crossed extensor reflex, and the knee jerk. Snider et al. (1949) showed with cats that cerebellifugal volleys directly inhibited spinal neurons, and Mollica et al. (1953) demonstrated that cerebellar stimulation inhibited reticular and vestibular neurons. Stella (1944) reported that acute ablation of the vermis did not affect inhibition from stimulation of the adjacent hemispheral portions of the anterior lobe. Inhibition of decerebrate rigidity occurred with dogs and cats only by stimulation of the hemispheral part of the culmen, while stimulation of the hemispheral part of the lobulus centralis produced an opposite facilitory effect.

With the advent of more sophisticated stimulators which allowed variations of frequency, pulse duration and waveform, new effects began to be observed. Working with decerebrate cats, Moruzzi (1948a-d) demonstrated that stimulation of the vermal surface of the anterior lobe produced results dependent on stimulus frequency: High frequencies resulted in inhibition, while low frequencies facilitated the rigidity. One millisecond rectangular pulses at rates of 30 to 300 Hz inhibited the hypertonus, with thresholds decreasing (down to 0.4-0.6 volts) as frequency was increased. At stimulus rates of 2 to 10 Hz and slightly higher intensities, the inhibitory effect was reversed to a slow increase in the extensor hypertonus rigidity without change of stimulus site or other stimulus parameters. Two possible mechanisms were postulated (Moruzzi, 1949) for the frequency dependency: Either excitatory and inhibitory neurons or neural circuits were intermingled within the cortex,

selectively responding to differing frequencies, or the same cerebellar units could be excitatory or inhibitory, dependent on the frequency of stimulation.

Similar effects were elicited by Terzuolo (1952, 1954) with curarized, decerebrate cats. After injection of tetanizing doses of strychnine, convulsive waves occurred in the electrospinogram at 10 to 20 Hz. Anterior lobe or reticular formation stimulation at 200 Hz blocked the convulsive waves, while 18 Hz stimuli increased their frequency. Cooling the cerebellum also intensified the convulsive activity. Nulsen et al. (1948), while mapping the motor homunculus of the anterior cerebellum, found that in the dog, monkey and chimpanzee (but not the cat), an increase in the cerebellar stimulus frequency resulted in facilitation rather than inhibition of the existing motor movement.

Moruzzi and Pompeiano (1957) found that stimulation of the vermal surface of the anterior lobe with parameters that normally evoked inhibition produced facilitation of the rigidity when the rostrolateral part of the ipsilateral fastigial nucleus had been lesioned. Since the spontaneous electrical activity and electrical excitability of the cortex was unaltered by the lesion, these findings were interpreted as apparently being due to the interruption of specific efferent pathways. They might also be interpreted as evidence that high frequency effects were mediated by fibers passing through the rostrolateral fastigial nucleus, while low frequency effects were mediated by other fiber tracts. Pompeiano (1958) also demonstrated that destruction of the rostral one-third of the interpositus nucleus rendered the intermediate part of the anterior lobe

completely inexcitable. These results, combined with those of Terzuolo and others, suggest that the inhibitory effects of cerebellar stimulation on decerebrate rigidity were mediated by fastigioreticulospinal pathways.

Cerebello-cerebral relationships

While the pathways and neural centers affected by cerebellar stimulation in the arrest of seizures are not presently known, the cerebrum is intimately associated with seizure activity, and connections between it and the cerebellum are of interest. Interconnections between the cerebellum and other central nervous system structures include the reticular formation (Terzuolo, 1952, 1954), as well as other prominent fiber tracts which pass either directly or indirectly to the vestibular nucleus (DeVito et al., 1956), tegmentum and sensory relay nuclei of the thalamus (Whiteside and Snider, 1953), red nucleus (Pompeiano, 1957), and cerebrum (Henneman et al., 1952). In 1938, Walker demonstrated that stimulation of the cerebellum of the cat increased both the amplitude and frequency of potentials recorded from the cerebral motor cortex. Dow (1942) showed that stimulation of the Sylvian regions of the cerebral cortex of the cat evoked action potentials in the culmen, simplex, ansiform, declive, tuber, paraflocculus and pyramis, and the above regions plus the uvula in the monkey. Henneman et al. (1952) mapped sensory areas on the cerebellar cortex which when stimulated produced potentials on corresponding sensory areas of the cerebral cortex. Cooke and Snider (1953) also demonstrated that cerebral stimulation can alter the electrocerebellogram. Dow et al. (1962) observed that cerebellar stimulation inhibited cerebral photic and auditory evoked potentials.

Whiteside and Snider (1953) described two ascending cerebellocerebral paths, one through the thalamic sensory relay nuclei, and one through the ascending reticular formation. Jansen and Jansen (1955) also described the reticular formation pathway in the cat, while Sasaki et al. (1976) described the cerebellothalmicocerebral pathway in further detail by demonstrating differing cerebral motor projections from the fastigial, dentate and interpositus nuclei in the monkey.

Cerebellar effects on seizure activity

Several neural centers have been seen to alter seizure activity: reticular formation (Fernandez-Guardiola et al., 1961), caudate nucleus (LaGrutta et al., 1971), median raphe nucleus (Kovacs and Zoll, 1974), and thalamus (Van Straaten, 1975). However, most interest has centered on the cerebellum. The relationship between the cerebellum and the epilepsies dates back to a clinical note in 1867 by Hammond where the coincidence of cerebellar pathologies and myoclonic epilepsy was noted. Hodskins and Yakovlev (1930) in a review of 300 epileptics pointed out a strong correlation between cerebellar atrophy and myoclonic epilepsy. Ten to fifteen percent of the 300 were cases of myoclonic epilepsy; of these one-third evidenced symptoms of cerebellar pathology and nearly all showed signs of cerebellar incoordination (sic).

Russell (1894) produced generalized convulsions by intravenous injection of absinthe in dogs, and noted an increase in ipsilateral convulsive activity after a unilateral cerebellar ablation.

Moruzzi (1941a-c) found that electrical stimulation of the vermal part of the anterior lobe of the cerebellar cortex with an inductorium

reduced movements induced by cerebral stimulation and the myoclonic twitches produced by the application of strychnine to the cerebral motor cortex. He later suggested (Moruzzi, 1950) that seizure discharges initiated in the cerebral cortex activated some unknown suppressor mechanism within the cerebellum which terminated the seizure activity.

Cooke and Snider (1955) electrically stimulated the cerebral cortex of curarized cats at 50-70 volts, 40-60 Hz for five seconds to induce generalized seizures, and antagonized them with cerebellar cortical stimulation at 40 volts and 300 Hz for five seconds (paramedian lobe). Stimulation at 12 Hz also alleviated the symptoms, but after, and not during the stimulation. Fastigial nucleus stimulation (30 volts, 60 Hz, 4 sec.) was also successful. In an effort to "delimit the mechanism" (Cooke and Snider, 1955, p. 20), several cerebellar afferents were also stimulated and found to be capable of antagonizing the seizure: inferior olive (7 volts, 60 Hz, 5.5 sec.), brachium pontis (20 volts, 12 Hz, 10.6 sec.), and brachium restiformis (40 volts, 20 Hz, 4.3 sec.). No further analysis was made of the pathways involved. The choice of stimulus parameters used was not explained, and may well have been arbitrary. High frequency cerebellar stimulation never facilitated seizures, but low frequencies occasionally did so.

Iwata and Snider (1959) stimulated the hippocampus of cats (5-15 volts, 1 msec biphasic, 100 Hz) to trigger seizures which could be partial (low voltage levels) or generalized (high voltage levels). Cerebellar cortical stimulation (tuber vermis, 7-20 volts, 30-150 Hz, 1 msec biphasic) routinely stopped the seizures.

Application of penicillin to the cerebral cortex creates a focal seizure pattern similar to that seen with cobalt powder (see below), developing progressively from intermittent spikes to focal or generalized convulsions. By stimulating the anterior cerebellar cortex at 250 Hz, 0.15-0.4 mA, 1 msec duration, Steriade (1960) was able, in cats, to suppress EEG spikes during the early development of the penicillin focus. However, the same stimulation of more developed foci resulted in facilitation. Kreindler (1962) also evoked penicillin seizures in cats, followed by stimulation at 2.5 Hz, 0.25-1.5 mA, 1 msec duration, applied to both the anterior and posterior cerebellar cortices. He was only able to achieve inhibition by stimulating before the seizure for 10-15 seconds at a high intensity (1.0-1.5 mA).

In 1962, Dow et al. did a study of focal seizures in rats caused by the application of cobalt powder to the frontal lobe of the cerebral cortex (see also Dow, 1974). They demonstrated that cerebellectomy or cooling of the cerebellum with dry ice significantly increased the seizure activity, a finding which was interpreted as support for earlier reports on the inhibitory effect of the cerebellum on seizures. Electrical stimulation of the cerebellum during cobalt-induced seizures revealed varying degrees of inhibition of the seizures, depending on the extent of damage by the cobalt. When cobalt was applied to the cortex, a characteristic pattern of development of abnormal EEG activity occurred (Dow, 1974). The electrical activity proceeded from paroxysmal slow waves to sharp waves to spikes to focal or generalized seizures. During the early stages of paroxysmal slow waves and sharp waves, Dow et al. (1962) were

able to consistently block this activity using stimulus parameters of 1-5 volts, 0.3-1.0 msec pulse width, 1-3 sec duration, and 200-400 Hz, applied with a bipolar electrode to all major areas of the cerebellar cortex, the white matter, or the cerebellar nuclei. During later stages, the stimulation was generally inhibitory, but it occasionally facilitated the abnormal seizure activity. Although the authors were vague about details, the facilatory effects may have been due to excessive destruction of the cerebral cortex by the cobalt. They stated that low frequency stimulation (20-50 Hz) gave inconsistent results, but did not give details or speculate on the cause. Their conclusion from these results was that for the given experimental conditions, ". . . the cerebellar influence on the development of chronic epileptic patterns is mainly of an inhibitory character" (Dow et al., 1962, p. 394).

Dow (1965) noted that afferent impulses from the periphery, connections from the hypothalamus, the caudate nucleus, the limbic system, and the reticular formation may under some circumstances produce a limiting influence on epileptic phenomena; however, the most common effect of electrical stimulation of these areas is an epileptic effect, and their ablation often enhances epileptic activity. He further stated that while cerebellar stimulation occasionally activates or aggravates a seizure, its predominant effect is to limit or terminate the convulsion.

In 1967, Reimer et al. attempted to duplicate the work of Dow et al. (1962) using cats, ". . . even though the epileptogenic effect of cobalt was found to be more transient in the cat than the rat" (Reimer et al., 1967, p. 456). Stimulating electrodes were inserted into the cerebellum

to an undisclosed depth, rather than being placed on the surface. Pulses of 0.1 msec duration, 4-300 Hz, and 1.0-7.5 volts were applied for 1-10 seconds, but no effects were seen except for an occasional aggravation or initiation of a seizure.

Possible explanations for the failures of Steriade (1960), Kreindler (1962), and Reimer et al. (1967) to routinely stop seizures may be found by examination of the stimulus parameters successfully used by Cooper (see below) (Cooper et al., 1973a,b); Cooper and Snider, 1974). Steriade exceeded the range of frequencies used by Cooper by more than a factor of ten and used current levels lower than Cooper's 0.5-3.0 mA range (Cooper and Snider, 1974). Kreindler used a very low frequency and the current that he considered to be very high was only half that used by Cooper. Reimer et al. used a pulse width of 0.1 msec, one-tenth that used by Cooper. Species variations, and electrode location, size and material, as well as the seizure type, may have contributed to the lack of success. The above three investigations employed chemically-induced focal seizures, while Cooper studied electrically-induced generalized seizures in monkeys and naturally-occurring epileptic seizures in man (mostly generalized).

In 1969, Mutani et al. investigated seizures produced by the application of cobalt to the hippocampus or amygdala in cats. Stimulation of the surface of the anterior vermis at 100 Hz, 6 volts, 0.6 msec for one second was sufficient to suppress interictal spikes for 10 seconds to 2 minutes after termination of the stimulus. During a seizure, stimulation at 6-13 volts could regularly halt the seizure if it were limited to the amygdala or hippocampus. If a seizure had spread to other subcortical

structures and the neocortex, cerebellar stimulation stopped seizures if applied after the seizure had developed, but had no effect when applied during its onset.

Grimm et al. (1970) used cobalt on the cerebral cortex of squirrel monkeys and stimulated the fastigial and dentate nuclei. The nuclei were stimulated at 10 Hz and 250-300 Hz, 0.1 msec, to determine threshold voltages that would cause EEG desynchronization (alertness); thresholds of 0.2-0.3 volts were observed. Monkeys with cobalt-induced seizures were then stimulated at three times the threshold levels (0.6-0.9 volts) with a cycle of three minutes on and three minutes off, for periods of 8-12 hours. Analysis of their data ". . . failed to identify any obvious effect of cerebellar stimulation upon amplitude, waveforms, or change in burst pattern" (Grimm et al., 1970, p. 134). If a comparison is again made with the parameters used by Cooper, the low voltages and short pulse width used by Grimm et al. may have been the cause for the negative results; the program of stimulation may have also contributed. Criteria for the selection of stimulus parameters and program were not given.

Hutton et al. (1972) used penicillin on the cerebral cortex of cats to induce seizures, as had Steriade (1960), stimulating the vermis and paramedian lobe of the cerebellar cortex, the dentate and interpositus nuclei, and grossly stimulating across the entire cerebellum, from one paramedian lobe to the other. Cerebellar cortical stimulation during the early stages of a focal seizure usually inhibited the spikes or reduced their frequency. Inhibition of a fully developed seizure could also usually be demonstrated. In more developed penicillin foci, less reliable

partial to complete inhibition of seizures could be achieved with stimulation. Dentate and interpositus stimulation partially inhibited spikes or reduced their frequency in over half of the experiments. Parameters of 200 Hz and 0.1-1.0 mA were used; pulse width was not reported. The cerebellum was also grossly stimulated at 0.3-5.0 volts; in four out of five experiments the spike frequency was decreased.

Cooper (1973) investigated the effect of chronic cerebellar stimulation on several neurological abnormalities in seven human patients. He reported his results as the following: "Anterior-lobe stimulation at 200 c/s and 10 volts has greatly decreased ipsilateral rigidity and/or spasticity in 3 patients. Stimulation of the same region at 10 c/s and 10 volts has ameliorated convulsive disorders in 4 patients. Follow-up in these 7 patients is one to six months." Subsequent investigations by Cooper and his associates have confirmed and extended these preliminary observations (Cooper et al., 1973a; Cooper et al., 1973b; Cooper and Gilman, 1973; Cooper et al., 1974; Cooper and Snider, 1974; Riklan et al. 1974), but no one set of parameters for stimulation has emerged as optimal. During the surgical procedure, multiple pairs of platinum disc electrodes are placed beneath the dura mater, over both the anterior and posterior cerebellar cortices bilaterally, for bipolar stimulation. Pulses of 1 msec duration at 7-15 Hz and 5-14 volts are applied after surgical recovery, and the optimum parameters and electrode combinations are empirically found (Cooper et al., 1974). Stimulation is applied continuously to alternating areas of the cortex, anterior to posterior, or left to right.

In addition to human studies, Cooper and Snider (1974) investigated in monkeys the effect of frequency variation on seizure arrest. Seizures were initiated by stimulation of various motor and sensory areas of the cerebral cortex with 40-60 Hz biphasic pulses ranging from 60-90 volts. Both human and monkey data strongly indicated that low frequency cerebellar stimulation (8-12 Hz) is effective in arresting seizures, both naturally occurring (humans) and electrically-induced (monkeys). High frequency stimulation (100-300 Hz) was found to prolong and aggravate seizures. The authors were unable to rationalize the discrepancy of these results with those of Moruzzi (1948a-d) and Dow et al. (1962). However, a recent clinical note (Cooper et al., 1976a) reported two patients in which 10 Hz stimulation was ineffective, while 200 Hz stimulation greatly reduced the frequency and severity of seizures.

Dauth et al. (1974) injected the anesthetic alpha chloralose into cats, creating an EEG pattern of "chloralose spikes" and high amplitude slow waves. The paramedian lobe of the cerebellar cortex was electrically stimulated, suppressing the effects of the chloralose. Four stimulus parameters (frequency, current amplitude, pulse duration, and pulse train duration) were varied independently in an attempt to delineate optimum parameter values. It was found that parameter values of 1-2 msec pulse duration, 100-200 Hz, and a 4-10 sec train duration, with inflection points near 1 msec, 90 Hz and 2.5 sec, were most effective in suppressing the spikes. Above a threshold level of approximately 2 mA, the stimulation current showed a roughly linear relationship to duration of EEG spike suppression.

Also in 1974, Myers and Bickford investigated chloralose-initiated myoclonic seizures in cats and attempted to duplicate the cerebellar stimulation sites used by Cooper (1973). Effects on the EEG were not discernible from the figures shown, but the EMG recordings of the myoclonic twitches showed that stimulation of the anterior cerebellar cortex at 100-200 Hz, 1 msec, and 2 mA completely suppressed the twitches, although it was followed by a rebound increase after stimulation. When stimulation was continued for more than 20 seconds, an escape phenomenon occurred as the myoclonus began to reappear. Suppression of the twitches and their electrographic correlates was also seen with posterior cortex stimulation, but the results were ". . . less marked than those obtained from the anterior position" (Myers and Bickford, 1974, p. 221). Stimulation at 1-10 Hz was ineffective, and facilitation of the myoclonus was also observed.

In an effort to resolve some of the discrepancies of reports on cerebellar stimulation where different methods of seizure initiation were used, Myers et al. (1975) examined the effects of both acute and chronic cerebellar stimulation for enflurane, pentylenetetrazol, penicillin, or chloralose seizures in cats. Enflurane (an inhalation anesthetic) inspired to deep levels of anesthesia, or intravenous pentylenetetrazol were used to trigger grand-mal-type seizures; penicillin given intramuscularly was used to model petit-mal epilepsy; and chloralose administered intraperitoneally was used to create myoclonic seizures. Cerebellar cortical stimulation (1-150 Hz, 0.1 msec, 2-15 volts constant voltage or 1-5 mA

constant current) was ineffective in blocking seizures. Again, this may have been due to the short pulse width (see above).

Babb et al. (1974a,b) investigated the two known ascending cerebellar efferent pathways using hippocampal cobalt seizures in the cat. Stimulation at points along the dentatothalamic pathways during seizures prolonged the seizure duration in four out of five cats, and terminated the seizure of a fifth cat during the clonic phase of the seizures. Stimulation along the fastigiobulbar pathways during ictus often terminated seizures during the clonic phase and shortened the average seizure duration in seven out of eight cats. The conclusion drawn from these results was that fastigiobulbar pathways are generally inhibitory and dentatothalamic pathways are generally excitatory to hippocampal cobalt seizures, although statistically the results were not conclusive. Stimulation parameters were 0.6 msec, 0.3-1.2 mA, and 5-100 Hz.

Snider (1974) investigated the effects of cerebellar stimulation on electrically induced seizures, both hippocampal and neocortical cerebral, using Macaca mulatta monkeys. Fastigial nucleus stimulation blocked hippocampal seizures (8 Hz, 0.8 mA, 5 sec, duration not reported) and neocortical cerebral seizures (10 Hz, 0.8 mA, 5 sec; 300 Hz, 1.0 mA, 5 sec). Stimulation of the cerebellar cortex, both paramedian lobe (10 Hz, 1.2 mA, 5 sec) and posterior folia of the culmen (10 Hz, 2.6 mA, 5 sec) blocked seizures induced by stimulation of the cerebral cortex. Local application of 2% Xylocaine to the cerebellar surface eliminated the effects of cerebellar stimulation.

Maiti and Snider (1975) found that stimulation of the vermis of rhesus monkeys for 10 seconds at 10 Hz, 8 volts, 1 msec could block electrically-induced hippocampal seizures, even when applied three minutes before the hippocampal stimulation. Cooling of the vermis of cats with a cryoprobe increased the duration of amygdaloid paroxysmal discharges from 6 seconds to as long as 79 seconds. In cats with bilateral fastigial nucleus destruction, hippocampal and amygdaloid seizures were lengthened and vermal stimulation was ineffective. When CNS catecholamine pathways were disrupted by the administration of 6-hydroxydopamine, vermal stimulation was again ineffective, indicating that the cerebellar inhibitory mechanisms are mediated through the fastigial nucleus and that catecholaminergic fibers are involved.

Hablitz (1976) tested the effect of cerebellar stimulation on generalized seizure activity initiated by large intramuscular injections of penicillin in cats. Stimulation was applied to vermal and paravermal areas of the cortex for alternating 10 second on and off periods at 10 or 100 Hz, 1 msec duration, and 0.25-2.0 mA. Significant decreases in both number and amplitude of paroxysmal bursts result; however, other arousing stimuli (unspecified) could also suppress the epileptiform discharges.

Summary of effective stimulus parameters

Reported stimulus parameters which inhibited seizure activity are collected in graphical form in Figure 4. In all of the reports of investigations of cerebellar stimulation, no rationalization was made for the choice of stimulation parameters, excepting those repeating the

Figure 4. Reported stimulus parameters inhibitory to seizure activity.

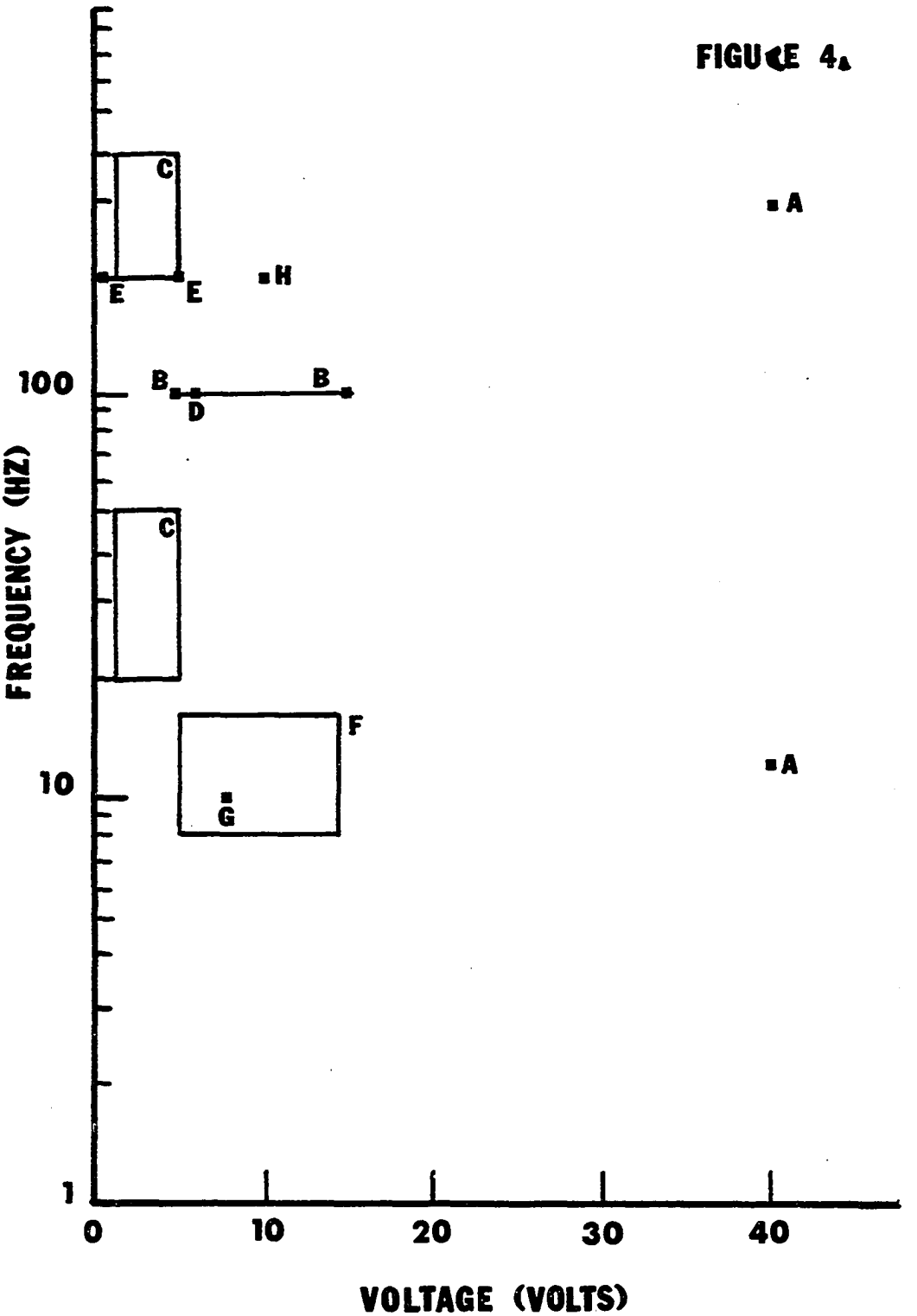
A. Stimulus intensity reported as voltage:

A	Cooke and Snider (1955)
B	Iwata and Snider (1959)
C	Dow et al. (1962)
D	Mutani et al. (1969)
E	Hutton et al. (1972)
F	Cooper (1973)
G	Maiti and Snider (1975)
H	Cooper et al. (1976a)

B. Stimulus intensity reported as current (p. 31):

A	Hutton et al. (1972)
B	Babb et al. (1974a,b)
C	Dauth et al. (1974)
D	Myers and Bickford (1974)
E	Snider (1974)
F	Hablitz (1976)

FIGURE 4.


C
A
H
E
E
100
B
B
D
C
FREQUENCY (HZ)
F
10
A
G
1
0
10
20
30
40
VOLTAGE (VOLTS)

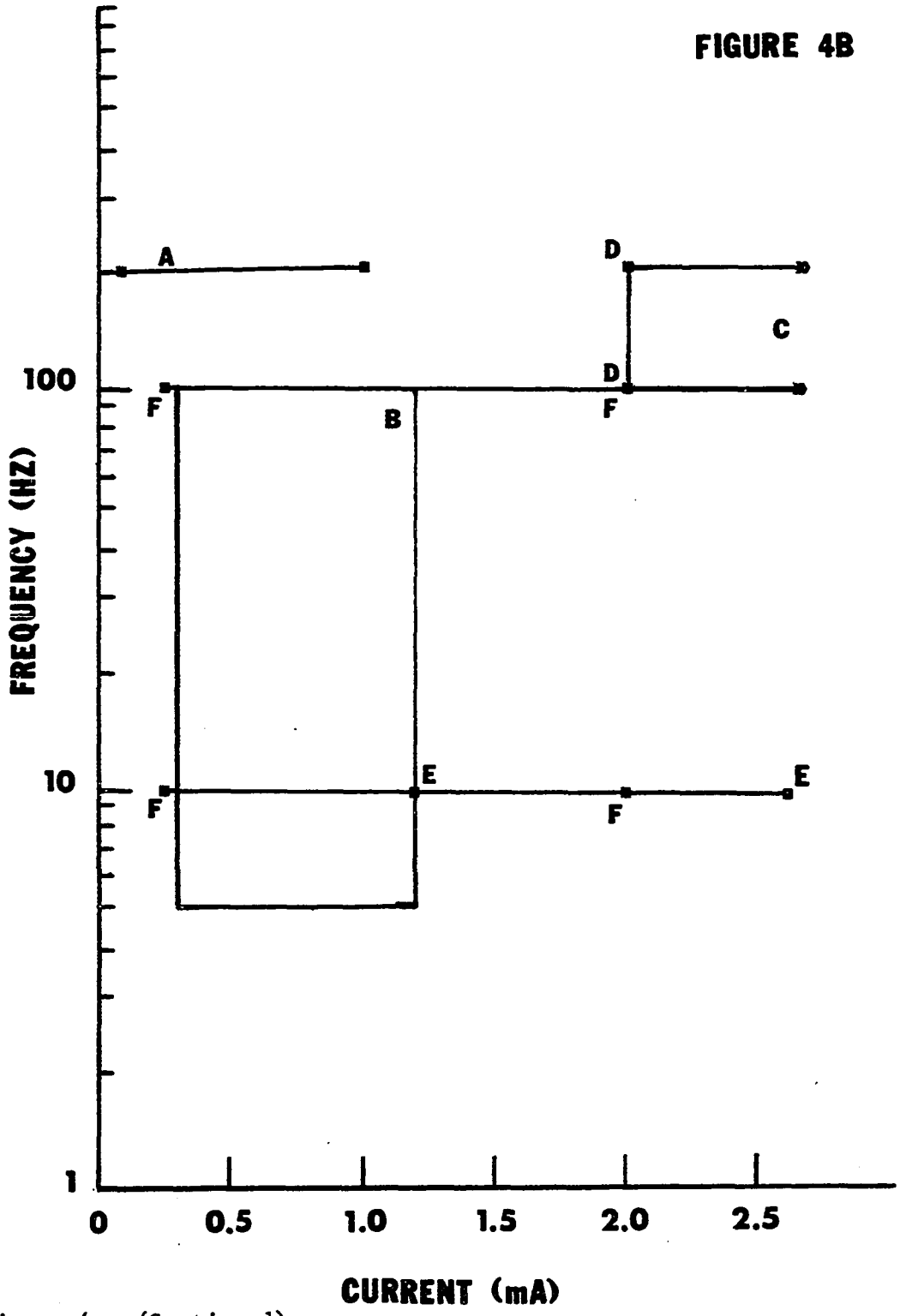


Figure 4. (Continued)

parameters used by Cooper (1973), and Cooper, who utilized a combination of values reported by Moruzzi (1950) and Dow et al. (1962). Nine reports mentioned pulse width values: five used 1.0 msec, two used 0.6 msec, one used 0.3-1.0 msec, and one used 1-2 msec. Although there is not a well-defined set of optimum stimulus parameters, it appears that intensities near 10 volts or 2 mA, and pulse durations near 1.0 msec have usually been sufficient. Effective frequencies are centered at 10 and 200 Hz. Of the investigations unsuccessful in affecting seizure activity, three (Reimer et al., 1967; Grimm et al., 1970; Myers et al., 1975) used pulse durations of 0.1 msec, a value found to be completely ineffective in the parametric study of Dauth et al. (1974) and confirmed by the results of other investigations. As a further confounding factor, stimulation must in some cases be chronically administered for periods of days to weeks before inhibitory effects are evidenced: With hippocampal alumina cream injections in Macaca mulatta monkeys, Babb et al. (1975, 1976) experienced a four day delay before beneficial effects on seizure activity began to occur, while Cooper et al. (1974) experienced similar delays lasting up to one month in human epileptics. Finally, Mutani et al. (1969) noted that it is impossible to exclude current spread to brain stem structures when stimuli exceed 5-10 volts. The criticism of possible current spread was voiced by both Dow and Moruzzi (1958) and Dow et al. (1962) with regard to the investigation of Cooke and Snider (1955), where levels as high as 40 volts were used. The spread of current to noncerebellar structures may provide an explanation for some of the above negative results.

Cerebellar damage

Concomitant with the use of cerebellar stimulation as a clinical therapy has been concern for the morphological implications of its use, particularly damage to neurons due to the stimulation. Tennyson et al. (1975), Gilman et al. (1975a), Gilman et al. (1975b) described the morphological effects of cerebellar stimulating electrodes on one Macaca mulatta monkey. Electrodes were found to be embedded in dense leptomeningeal (pia and arachnoid) reactive tissue, and examination of underlying cortex revealed loss of Purkinje cells and ultrastructural alterations. A lesser degree of cell damage was found beneath nonstimulating control electrodes.

Larson et al. (1976) stimulated the cerebellar cortex in monkeys in order to measure current density distributions and investigate possible alterations in the blood-brain barrier (BBB), and then implanted stimulating electrodes in humans for the treatment of spasticity and dyskinesia. After stimulating monkey cerebellar cortices, Larson et al. were not able to observe changes in the BBB or loss of Purkinje cells after 17 hours of stimulation at 4 mA, 100 Hz, and 0.25 msec. However, after two minutes at 5 mA, definite damage to the BBB was seen (evidenced by the escape of Evans blue dye from capillaries), and cell loss was observed bilaterally as deep as 3 mm below the surface. Only light microscopic examination was performed. Human studies showed improved gait, speech, and ability to sit without support.

Brown et al. (1976, 1977) and Babb et al. (1977) found some thickening of the leptomeninges, slight thinning of the subjacent molecular layer

and decreased Purkinje cells beneath nonstimulating control electrodes in monkey studies after 205 hours of stimulation at 10 Hz, 1 msec biphasic, 2.4-22.0 μcoul/phase. Stimulating electrodes produced changes in pia, arachnoid, subjacent Purkinje cells, dendritic arborization, parallel fibers, and associated synapses in the molecular layer. Damage to non-stimulated cortex was attributed to mechanical compression of the molecular layer and pial vessels. At a stimulus intensity of 0.5 μcoul/phase, no damage attributable to the stimulation could be demonstrated. Injury to the cortex was proportional to stimulus intensity, and dependent on charge density rather than total charge or current.

Cerebellar atrophy and cortical degeneration have frequently been associated with epilepsy and anticonvulsant medications, even to the point of nearly complete loss of Purkinje cells (Afifi and Van Allen, 1968). Rajjoub et al. (1976) compared Purkinje cell densities in cerebellar cortical tissue from autopsied control patients (N=5), autopsied epileptic patients (N=4), and biopsies from epileptic patients taken at the time of implantation of cerebellar stimulating electrodes (N=3). The Purkinje cell density of the eight epileptic patients averaged 38% of the density found in the five normal cerebella. Of the three stimulated (10 Hz, 3-12 mA, 1 msec capacitively-coupled monophasic) patients, the two with severe Purkinje cell loss experienced better seizure control than the third, who only had mild Purkinje cell loss. However, the third patient also achieved improved seizure control.

Cooper et al. (1976a) biopsied five patients at the time of implant of cerebellar stimulating electrodes. Findings under light microscopic

examination were decreased thickness of the molecular layer, decrease in numbers of stellate, basket, granule and Golgi cells, and a marked decrease or absence of Purkinje cells. One patient who died of unrelated causes after 17 months of unsuccessful cerebellar cortical stimulation was also examined for cortical damage. The left posterior cerebellar cortex, which had not been stimulated or surgically exposed, revealed unthickened pia matter, thinning of the molecular and granular layers, and complete absence of Purkinje cells. Cortex subjacent to the stimulating electrodes (anterior lobe) had moderate thinning of the molecular layer, loss of stellate, basket and granule cells, and 50-100% loss of Purkinje cells, with no evidence of damage to pia or adjacent cortex. However, comparisons between anterior and posterior cortex biopsies may not be meaningful in light of Meldrum's (1974) observation that Purkinje cell loss in epilepsy occurs predominantly in the posterior lobe.

Mechanisms and pathways

The mechanisms whereby cerebellar stimulation stops, prevents, or reduces seizures are unclear. However, because of the anatomy and physiology of the cerebellum, the effect is probably related to a change in the code of efferent impulses occurring at the level of the cerebellar nuclei: increases or decreases in frequency, or more complex patterns. Three possible effects on the cerebellar nuclei cells from the cerebellar cortex are 1) an increase or 2) a decrease in the inhibitory impulses from Purkinje cell axons, or 3) excitatory antidromic pulses on axon collaterals of mossy and/or climbing fibers. Bantli et al. (1974) have suggested that if Purkinje cell output is increased, the effect may be either

mediated by inhibition of a direct loop between the cerebrum and the cerebellum, or by an effect on the reticular formation and/or the non-specific nuclei of the thalamus. Kreindler (1962) noted that lesions of some thalamic nuclei (anterior, central, and centre median) resulted in increased duration of penicillin seizures in cats. However, the results of Babb et al. (1974a,b) tend to rule out the dentatothalamic path in favor of fastigiobulbar pathways. Further, Eccles et al. (1975) demonstrated monosynaptic EPSP's from the fastigial nucleus to neurons in the medullary reticular formation, and Gloor and Testa (1974) and Testa and Gloor (1974) showed with generalized pencillin seizures in cats that increased reticular formation activity decreased or abolished convulsive discharges, while decreased reticular activity facilitated seizures. Hablitz (1976) stimulated the mesencephalic reticular formation (10-30 Hz, 1 msec, intensity not reported) and found inhibition of generalized penicillin epileptiform activity in cats.

Bantli et al. (1974) also suggested that cerebellar stimulation could be activating mossy fibers, whose activity would decrease the inhibitory output of the Purkinje cells, with a resultant increase in the activity of the cerebellar nuclei. Antidromic conduction of these mossy fiber impulses could be stimulating the same or other cerebellar nuclei cells, or even reticular or thalamic cells, via axon collaterals.

Cooper and Snider (1974) proposed that 10 Hz stimuli may be slow enough to allow Purkinje cells to escape the normally-occurring inhibition by basket, stellate and Golgi cells, thus transmitting a 10 Hz burst of inhibition to the cerebellar nuclei which would be functionally projected

to higher centers; this burst might then be adequate to desynchronize the seizure frequencies. Partial support for this proposal may lie in the discovery by Wagner et al. (1975) that cerebral cortical epileptiform activity can be suppressed by generalized and localized cortical desynchronization. Investigators as early as Walker (1938) have reported cortical desynchronization due to cerebellar stimulation.

Grabow et al. (1974) suggested that the disinhibition observed by Ito et al. (1964) in cerebellar nuclei cells could provide an alternative explanation of the mechanisms of cerebellar stimulation. Stimulation at 10 Hz may trigger bursts from Purkinje cells, which are shut off immediately by basket, stellate and Golgi cell activity. The abrupt termination of inhibition from the Purkinje cells would result in disinhibition (removal or reduction of background inhibition, effectively acting as an excitation). The prolonged hyperpolarization of cerebellar nuclei cells by the Purkinje cells is followed by a late depolarization of several hundred milliseconds duration. The disinhibition may be of sufficient magnitude to trigger a train of excitatory impulses from the nuclei. Disinhibition provides a means whereby the purely inhibitory projection from Purkinje cells can control their targets, the cerebellar nuclei cells, with both inhibition and facilitation.

Several observations from investigations where cerebellar stimulation was not employed provide indirect evidence of an increased Purkinje cell firing rate with cerebellar stimulation. Julien (1974) and Julien and Halpern (1972) examined the effects of diphenylhydantoin (DPH) and other antiepileptic drugs on epileptiform activity (penicillin applied topically

to the cerebral cortex) and Purkinje cell discharge rates. DPH has been shown to limit the spread of seizure activity rather than suppressing the focus. Its mechanism suggests a reinforcement of those systems within the brain which serve to limit seizure propagation, rather than a direct effect on epileptic tissue as such (Woodbury, 1969). In addition, it has often been claimed that long-term administration of high doses of DPH can cause cerebellar ataxia and destruction of Purkinje cells, although Dam (1972) has disputed Purkinje cell losses with DPH. With single-cell recordings using microelectrodes, Julien (1974) found that the administration of DPH dramatically increased the discharge rate of Purkinje cells, followed by a decrease in the discharge rate of cells within Dieter's (vestibular) nucleus. Subsequent experiments indicated that phenobarbital and diazepam similarly increase Purkinje cell discharge rates, while carbamazepine does not.

Also, Mitra and Snider (1975) demonstrated an increase in Purkinje cell activity in the tuber vermis after hippocampal afterdischarges, which accelerated during the afterdischarges and could last for several seconds after the end of the hippocampal activity. Their recordings indicated that hippocampal seizure activity is relayed to the cerebellum via the nucleus tegmenti pontis, while neocortical seizure activity is relayed through the pons, inferior olive, and lateral reticular nucleus, rather than through the nucleus tegmenti pontis.

Conversly, Andersen et al. (1964) measured large IPSP's in Purkinje cells after surface stimulation to the lobulus simplex. Stimulation at 10, 16 and 100 Hz reduced Purkinje firing from a spontaneous rate of

200 Hz to complete cessation for 100, 120 and 150 msec respectively after each stimulus.

Wood et al. (1976b) found with human epileptics that cerebellar stimulation reduced cerebrospinal fluid concentrations of gamma amino-butyric acid (GABA). Since GABA is the putative neurotransmitter of Purkinje cells, Wood et al. suggested that this might reflect Purkinje cell degeneration near the electrodes. However, they also suggested (Rajjoub et al., 1976) that it could be an indication that Purkinje cell discharge is depressed during cerebellar stimulation. Also, in their limited study Rajjoub et al. found that two patients with severe Purkinje cell loss achieved better seizure relief with cerebellar stimulation than one patient with relatively mild Purkinje cell loss.

Wood et al. (1976a,c) also found elevated CSF norepinephrine (NE) levels after cerebellar stimulation in humans. Since decreased NE brain levels increase seizure susceptibility (Browning and Maynert, 1970) and increased NE levels reduce seizure susceptibility (Feldberg and Sherwood, 1954), Wood et al. ascribed anticonvulsant activity to NE and suggested that cerebellar stimulation suppression of seizure activity is mediated by synaptic release of NE. Decreased GABA with cerebellar stimulation (see above) may directly result from NE, since microiontophoretic application of NE to cerebellar Purkinje cells arrests their tonic firing (Hoffer et al., 1971). Neural sites implicated as a source of the NE (Wood et al., 1976c) are locus coerulus innervation of the cerebellar cortex (Nakamura and Iwama, 1975), post-ganglionic terminals innervating cerebellar blood vessels (Dahi and Nelson, 1964), antidromic activation of the reticular

formation by climbing or mossy fibers (Bloedel and Burton, 1970), and stimulation of cerebello-rubro-reticular projections and nonspecific thalamic nuclei (Bantli and Bloedel, 1975).

Elevation of seizure threshold by cerebellar stimulation

Englander et al. (1975) and Johnson et al. (1976) attempted to quantify the seizure suppressive effects of cerebellar stimulation in studies of the augmenting response of the thalamocortical motor (TCM) system of the cat. Pulse pairs were delivered to the ventrolateral thalamus at a rate of one pulse pair per second, and the evoked response from the second pulse (the augmented response) was measured from a recording electrode array placed over the ipsilateral sensorimotor cortex. With the pulse amplitude held constant and the interpulse interval sequentially increased from 70 to 500 msec, an excitability curve of response amplitude versus pulse pair interval was produced. The resultant curve was roughly bell-shaped, with a faster rise than fall, and maximum amplitude at pulse intervals of 200-300 msec. In addition, threshold curves were obtained by holding the pulse pair interval constant at 200 msec and increasing the stimulus pulse pair amplitude. These curves (response amplitude versus stimulus amplitude) consisted of a horizontal line followed by a ramp beginning at the threshold stimulus amplitude.

The effects of cerebellar stimulation on the excitability of the TCM system were compared with the effects of anticonvulsant drugs. Previous studies (Johnson et al., 1975) showed that an unstable condition in the TCM system is indicated by an increase in both the height and duration of the excitability curve. Cortical epileptiform activity (chloralose

spiking) showed a strong correlation with increased height and duration of the excitability curve. Constant current stimulation of the contralateral paramedian lobe of the cerebellar cortex was performed with continuous unidirectional pulses of 1 msec duration, 10 or 100 Hz, and 100 μA to 1 mA currents. It was found that DPH, diazepam, or cerebellar stimulation at a frequency of 100 Hz reduced the height of the excitability curve and raised the response threshold to thalamic stimulation. Cerebellar stimulation at 10 Hz or ethosuximide reduced the duration of the excitability curve. Carbamazepine had an effect different from the other drugs tested; however, this effect was not described. DPH was administered intravenously until no further reduction in the excitability curve was achieved. The total dose was 80 mg/kg (serum concentration of 64 μg/ml), an extremely toxic level if maintained chronically. Under these conditions, the excitability curve was reduced to approximately 52% of the control. The maximum effect was approximately equivalent to the results found from cerebellar stimulation at 100 μA (the DPH curve was 15% below the 100 μA curve). The curve reductions due to 250 and 500 μA cerebellar stimulation greatly exceeded that obtained with DPH, and in most cases intensities of 1 mA completely suppressed the excitability curve. The minimum effective stimulus intensity was found to be 10 μA.

None of the anticonvulsant drugs tested had any appreciable effect on the threshold value of the threshold curve, but they did reduce the slope of the ramp portion. Cerebellar stimulation (100 Hz) reduced the slope and had extensive but variable effects on threshold, depending on the pulse pair interval. Johnson et al. (1975) were not able to demon-

strate whether the cerebellar effects upon excitability and threshold occurred in the thalamus, the cerebellar cortex, or both, nor were they able to determine the pathways over which the changes were effected.

The above results indicate that cerebellar stimulation is potentially more effective than anticonvulsant drugs in reducing the excitability of the CNS, as measured by the thalamocortical motor system augmenting response. However, the investigations were performed on animals not subject to seizure activity. In addition, there is some doubt that the thalamus plays a direct role in the amelioration of seizure activity by cerebellar stimulation (cf. Babb et al., 1974a,b, and Mitra and Snider, 1975). Although dentatothalamic pathways have been found ineffective, there has been no evidence to rule out pathways from the bulbar reticular formation to the thalamus.

Convulsant and Anticonvulsant Mechanisms

Seizure activity was induced both electrically and chemically in this study, and suppressed chemically with two drugs in addition to the cerebellar stimulation discussed above. The implementation of these treatments is described in Methods and Materials below. Seizure activity was chemically induced by intravenous pentylenetetrazol (pentamethylenetetrazol, pentetrazol, METRAZOL, LEPTAZOL, CARDIOZOL, NIORIC), a synthetic convulsant herein abbreviated PTZ. The convulsant activity of PTZ has been thought to result from an increase in neuronal excitability, but the mechanisms are unknown. Experimental evidence (Esplin and Zablocka-Esplin, 1969) indicates that the effect may be due to a decrease in the

time for synaptic recovery, which would augment on-going repetitive neuronal activity without influencing nonrecurrent activity (impulses occurring at frequencies too low to be influenced by variations in refractory period durations). However, Stone (1976) demonstrated that microiontophoretically-applied PTZ depressed the firing rates of 101 of 116 rat cerebral cortex neurones, exciting only 6. He suggested that PTZ might have both excitatory and inhibitory direct effects, and that the inhibitory effects might act on normally-inhibitory cells, decreasing overall inhibition and increasing ongoing activity (disinhibition).

Transhemispheral electrical stimulation of the frontal cerebral cortices was the second technique utilized to induce seizure activity. Electrically-induced seizures are unquestionably initiated by the synchronous activation of large populations of neurons by suprathreshold stimuli. However, the mechanisms whereby the hypersynchronous discharges are maintained after termination of the stimulation are unknown. A predominance of cholinergic pathways appears to be involved, since electrically-induced seizures are followed by the appearance of acetylchline (ACh) in the normally ACh-free cerebrospinal fluid, and by elevated cholinesterase levels (Karczmar, 1974; Fink, 1966, 1974). Further, the behavioral and electrographic changes following electroconvulsive therapy in human patients are blocked by the administration of anticholinergic drugs such as atropine (Fink, 1966). Local elevations of ACh levels from the stimulation may be adequate to exceed the hydrolysis capabilities of endogenous cholinesterases, resulting in sustained firing

of cholinoceptive neurons, further elevating free ACh levels (Fink, 1966). In addition, the possible role of massive releases of other neurotransmitters (serotonin, norepinephrine) in response to the stimulation cannot be discounted (Fink, 1974). However, the observation that elevated norepinephrine levels reduce seizure susceptibility (Feldberg and Sherwood, 1954) indicates that the mechanisms of electrically-induced seizures remain essentially unresolved.

Seizure activity was chemically suppressed with two anticonvulsant drugs, phenobarbital (phenobarbitone, LUMINAL, PROBITAL, GARDENAL, SENTAL) and diphenylhydantoin (phenytoin, DILANTIN, EPTOIN), abbreviated DPH. The complete mechanisms of action of phenobarbital are unknown despite extensive investigation (Woodbury, 1969). It has been shown to inhibit posttetanic potentiation (PTP), reduce transmission during repetitive discharge, and depress certain pathways with low transmission safety factors. The effects may be accomplished by a prolongation of neuron action potentials to several hundred milliseconds, brought about by a blockade of a conventional potassium-dependent cell repolarization by interference with a voltage-dependent calcium current into the cell necessary for activation of the repolarization (Kleinhaus and Pritchard, 1976). A second mechanism which may be affected is the normal sequestering of intracellular calcium by mitochondria. The increased intracellular calcium levels produced by interference with this calcium pathway increases the cell membrane potassium conductance, which depresses neuronal excitability and reduces the response to ACh, which in the cerebral cortex acts by decreasing potassium conductance (Krnjevic, 1975). Clinically pheno-

barbital is effective in grand-mal and tonic-clonic focal seizures, status epilepticus, and withdrawal seizures. Anticonvulsant effects often occur only at levels also producing sedation.

DPH has been studied clinically and experimentally more thoroughly than any other antiepileptic drug (Woodbury and Fingl, 1975; see Bogoch and Dreyfus, 1970, 1975). It has been shown to produce its anticonvulsant effects by stabilizing excitable membranes and depressing the spread of repetitive activity by blocking PTP (Woodbury, 1969). The stabilization has been attributed to enhanced active sodium transport out of the cell due to increased availability of high-energy phosphates (Woodbury and Kemp, 1971). However, more recent evidence suggests that it may be due instead to a reduction by DPH of the inward sodium ion flow during action potentials and excitatory postsynaptic potentials (Johnson and Ayala, 1975). DPH is used clinically in the treatment of grand-mal, psychomotor, and symptomatic seizures.

METHODS AND MATERIALS

General

Acute experiments were carried out with adult, male, New Zealand albino rabbits[1] weighing approximately 2.5-3.5 kg. The animals were housed in general animal holding facilities, one or two to a cage, with water and standard rabbit pellets available ad libitum, and a lighting schedule beginning at 8 AM for eight hours. Animals were prepared and recordings generally begun by 10 AM and ended by 5 PM.

Physiological Methods

The rabbits were immobilized on a restraint board fitted with a head holder. The scalp was incised along the midline from the nasion to the upper cervical region with the blade of an electrocautery unit.[2] The periosteum was removed and the scalp and musculature retracted with a self-retaining Weitlaner retractor[3], and tissue and bone hemorrhage were controlled with the cautery and bone wax[4] respectively. The skull was trephined with a No. 51 drill held in an X-Acto model maker's pin vise.[5]

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[1]Porter's Rabbitry, Box 582, Dayton, Iowa 5530.

[2]Wappler Cold Cautery Scalpel, Model C-450, American Cystoscope Makers, Inc., Stanford, Connecticut 06902.

[3]SU-3110, V. Mueller, Chicago, Illinois 60648.

[4]Lukens Bone Wax, ASR Medical Industries, St. Louis, Missouri 63108.

[5]X-Acto, Long Island City, New York 10011.

The drill diameter matched that of the electrode barrel so that the electrode assembly was held rigidly in the trephined hole by friction and no further fixation was required.

Concentric tripolar electrodes were used for recording (see Appendix A). They consisted of an outer barrel (1.0/1.5 mm inner/outer diameters) of stainless steel for cortical recording, and an inner pair of twisted 0.01 inch, formvar-insulated stainless steel wires[1] for depth recording. The stainless steel barrel, encased in a brass hub, extended 2 mm from the distal end of the hub. The depth electrodes were precut to appropriate lengths and 0.5 mm of the tips cleaned of insulation, beveled and separated by 1-2 mm. The remaining insulation was protected from the barrel by a length of polyethylene tubing (PE #60)[2] cut to the same length as the barrel. The depth electrodes and PE tubing were fastened within the cortical electrode with denture acrylic.[3] After implantation the brass hub rested on the skull and the barrel was in contact with the meninges and/or cortex. Completed electrodes could be repeatedly used. For further detail see Van Meter (1969). Stimulating electrodes were constructed using the same barrel and hub assembly with an inner silver ball electrode and insulating polyethylene tubing (Appendix A). The silver ball electrode was formed from a one inch length of 0.033 inch diameter

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[1]Driver Harris, Ltd., Harrison, New Jersey 07829.

[2]Intramedic Polyethylene Tubing, Clay Adams, Div. of Becton, Dickinson and Co., Parsippany, New Jersey 07054.

[3]Hygenic Dental Manufacturing Co., Akron, Ohio 44310.

silver wire[1] heated in a flame until a smooth ball of approximately 1.5 mm diameter was formed at the tip.

Electrodes were manually implanted using stereotaxic coordinates from the atlas of Sawyer et al. (1954) (Table 2), with the intersection of the mid-sagittal and coronal bone sutures serving as the anterior/posterior and lateral origins. Cerebellar cortical stimulating electrodes were implanted at the articulation of the parietal, interparietal and supra-occiptal bones.

Animals were placed in a dimly lighted enclosure designed to shield from radio frequency and other electromagnetic interference.[2] Recordings were made with a six channel Grass Model 7 Polygraph[3] and were initiated thirty to sixty minutes after all surgical procedures had been completed. Bipolar recordings were made between left anterior cortex and basal olfactory area (LAC-BOA), right anterior cortex and lenticular nucleus (RAC-LN), left posterior cortex and hippocampus (LPC-HPC), right posterior cortex and hippocampus (RPC-HPC), left anterior dorsal thalamic nuclei and right brain stem reticular formation (THAL-RF), and right anterior cortex and left posterior cortex (RAC-LPC). EEG desynchronization response to the sensory stimuli of touch, sound and pain were observed after the surgical recovery period to detect gross neurological damage from electrode implantation (Van Meter, 1969). Electrode placement was histologi-

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[1]Fischer Scientific Co., Chicago, Illinois 60651.

[2]Universal Shielding Corp., Plainview, New York 11803.

[3]Grass Instrument Co., Quincy, Massachusetts 02169.

Table 2. Electrode stereotaxic coordinates[a]

Location	Anterior (+) Posterior (-)	Lateral	Depth
Recording:			
BOA	+4.0	6.5	12.0
LN	+2.0	6.5	9.0
THAL	-3.0	1.5	10.0
LHPC	-4.5	6.5	4.5-5.5
RHPC	-4.5	6.5	4.5-5.5
RF	-8.5-9.0	2.0	12.0
Stimulating:			
Cerebellar	-20.0	5.0	0.0
Cerebral	+10.0	4.0	0.0

[a]Coordinates given in mm, for New Zealand albino rabbits of 2.5-3.5 kg body weight.

cally verified in two preparations using frozen, unstained, 50 μm sections and the stereotaxic atlas of McBride and Klemm (1968). Sections were mounted without fixation and visually examined with a light microscope.

All surgical procedures were performed under 1% lidocaine local anesthesia.[1] Although high doses of lidocaine may produce CNS excitation and convulsions (Ritchie and Cohen, 1975), the maximum subcutaneous/ intramuscular dose used in these experiments (0.02 mg/kg) was lower by a

[1]Astra Pharmaceutical Products, Inc., Worcester, Massachusetts 01606.

factor of at least 250 than the minimum intravenous dose of 5 mg/kg found to produce EEG effects (Kovalev, 1960). Two limbs served as leads for the EKG, which was monitored with a portable CRO EKG device.[1] All rabbits were euthanized by an intravenous overdose of pentobarbital[2] at the termination of the experiments.

Seizure Induction Methods

Intravenous pentylenetetrazol (PTZ)[3] or direct electrical stimulation of the anterior motor cortex with a Grass Model S88 stimulator[4] and Grass Model SIU 5 stimulus isolation unit[4] at 50 Hz, 1 msec pulse duration and 2 second train duration was used to evoke generalized seizure activity. Electrically-induced generalized myoclonic seizures of 20-60 seconds duration were evoked. Stimulus intensities were increased at fifteen minute intervals until the desired seizure duration was obtained. Pentylenetetrazol seizures were induced by intravenous injections of 10 and 15 mg/kg, to produce petit-mal and grand-mal EEG seizure patterns.

For repeated injections, the lateral ear vein was cannulated with a one inch, 22 or 20 gauge disposable needle, held in place with a bulldog clamp[5], connected to a three-way stopcock[6] with two male luer-to-hose-end

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[1]Model 412 Monitor, Tektronix, Inc., Beaverton, Oregon 97005.

[2]Med-tech, Inc., Elwood, Kansas 66024.

[3]Knoll Pharmaceutical Co., Whippany, New Jersey 07981.

[4]Grass Instrument Co., Quincy, Massachusetts 02169.

[5]CH-5312, V. Mueller, Chicago, Illinois 60648.

[6]HY-23138, V. Mueller, Chicago, Illinois 60648.

connectors.[1] An injection syringe (1 or 2 1/2 cc) was connected to the second stopcock opening and a 10 cc syringe with heparinized saline for washing in drugs was connected to the third. The stopcock was affixed with resin glue to a Plexiglas tube and clamped to the restraint board.

Anticonvulsant Treatment Methods

Seizures were antagonized pharmacologically with diphenylhydantoin (DPH)[2] or phenobarbital[3] injected thirty minutes prior to inducing seizure activity. Although peak plasma levels after oral administration may not occur for three to twelve hours (Woodbury and Fingl, 1975), more rapid effects are achieved by intravenous administration (Meyers et al., 1972). The doses used for the anticonvulsant drugs (Barnes and Eltherington, 1973) were: phenobarbital, 25 mg/kg body weight IV, and DPH, 30 mg/kg IV. Phenobarbital (50 mg/ml) was dissolved in distilled water, while diphenylhydantoin sodium (50 mg/ml) was prepared as a solution of 40% propylene glycol, 10% ethyl alcohol, and 50% water adjusted to pH 12 with sodium hydroxide to keep the DPH in solution.

Cerebellar stimulation was applied across the cerebellar hemispheres with a Grass Model SD9 stimulator[4], with silver ball electrodes located on the simplex and ansiform lobe regions of the hemispheres. Stimulation

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[1] HY-23068, V. Mueller, Chicago, Illinois 60648.

[2] Parke, Davis & Co., Detroit, Michigan 48232.

[3] Merck, Inc., Rahway, New Jersey 07065.

[4] Grass Instrument Co., Quincy, Massachusetts 02169.

sites anterior to the simplex and ansiform lobes were limited by the posterior extension of the superior sagittal sinus and the transverse sinuses. The stimulation waveform consisted of a pair of charge-balanced, capacitively coupled biphasic pulses, with the positive pulse leading the negative. See Results for stimulation parameters.

Large stimulus artifacts in the EEG tracings during cerebellar stimulation were examined to determine whether they masked or added to EEG seizure activity. A 2 Hz sinusoidal voltage from a sine wave generator applied between the lenticular nucleus electrodes in a euthanized rabbit was seen to add to the 10 Hz cerebellar stimulation artifact. Thus, with the "artificial EEG" it was established that the effects of cerebellar stimulation could be evaluated visually with the artifact present.

Experimental Protocol

The first part of this research consists of the replication of PTZ and electrical stimulation of the cerebral cortex as models of seizure activity in the rabbit (Longo, 1962; Purpura et al., 1972), and the determination of parameters for cerebellar stimulation that block or reduce the intensity of this seizure activity.

Elevation of seizure thresholds was evaluated in the second part by antagonizing PTZ and electrically-induced seizures with DPH, phenobarbital and cerebellar stimulation. DPH does not affect PTZ seizures (Cutting, 1972), therefore five combinations of convulsant and anticonvulsant treatments resulted. A minimum of five animals was used for each of the five combinations.

Control seizures were obtained in each experiment, which for PTZ seizures consisted of the administration of both seizure doses (10 and 15 mg/kg), while for electrically-induced seizures the control was a myoclonic seizure of 20-60 seconds duration. The anticonvulsant treatment was given and the convulsant treatment reapplied with constant increments (2 or 3 mg/kg, or 0.1 or 0.2 volts, depending on the initial response of the animal) until a seizure similar to the control seizure was obtained. The resulting increase in PTZ dosage or stimulation voltage was designated the seizure threshold elevation ΔT_s.

Statistical Methods

Tests of the significance of the elevation of seizure thresholds were made using the standard t-test, while comparisons between blocks of experimental data were made with the modified t-test, the statistic for populations where the standard deviations (σ) are unknown and different (Walpole and Myers, 1972). The population distributions were assumed to be approximately normal. The degrees of freedom for the modified t-test are given by:

$$\nu = \frac{(s_1^2/n_1 + s_2^2/n_2)^2}{\frac{(s_1^2/n_1)^2}{n_1-1} + \frac{(s_2^2/n_2)^2}{n_2-1}}$$

and the t value is given by:

$$T' = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{s_1^2/n_1 + s_2^2/n_2}}$$

where

s = estimated standard deviation

$\overline{X}$ = estimated mean

n = number of observations

Tests were made on the null hypothesis that the means are equal (H_o: $\mu_1 = \mu_2$), with the alternative hypothesis that one mean is larger than the other (H_1: $\mu_1 > \mu_2$). The critical region for rejection the null hypothesis is $T > t_p$, where t_p is taken from a table of critical values for the t distribution for a given level of significance p, and given degrees of freedom, ν. Since the value of ν calculated from the above formula is seldom an integer, the values calculated were rounded off to the next lower integer to allow the use of standard tables.

RESULTS

Electroencephalographic responses following intravenous PTZ are shown in Figure 5. The physiological and electrophysiological responses to the 10 and 15 mg/kg doses agreed with those reported by Longo (1962). A dose of 10 mg/kg produced the generalized EEG spike-and-wave complex characteristic of petit-mal epilepsy with no concomitant motor activity. Doses of 15 mg/kg or greater evoked a brief period of desynchronization followed by large (300-600 μV) voltage spikes which appeared in the brain in a sequence progressing from rostral to caudal regions, gradually decreasing in frequency with time from roughly 20 to 2 Hz. After 30-60 seconds of this activity, post ictal depression ensued with a characteristic isoelectric baseline. EEG activity resumed within thirty seconds as a period of high (500-1000 μV) voltage slow (2-3 Hz) waves, during which short seizures could occur. The high voltage fast spikes coincided with a tonic convulsion, while the slower spikes were accompanied by clonic convulsions. This sequence of events resembled the clinical pattern of a grand-mal seizure. In addition to the responses reported by Longo (1962), a myoclonic twitch usually appeared 4-5 seconds after the 10 and 15 mg/kg doses of PTZ (Figure 5A). The duration and severity of EEG responses to given doses of PTZ varied from animal to animal, and each animal served as its own control. Responses to PTZ doses of 5 mg/kg were not as distinctive and easily recognized as responses to 10 and 15 mg/kg doses. Responses to 5 mg/kg PTZ consisted of 3-5 Hz, 300-400 μV bursts in the associative cortex lasting 2-4 seconds, which were replaced by desynchroniza-

Figure 5. Electroencephalographic responses to intravenous pentylenetetrazol (PTZ).

A. Response to 10 mg/kg injection of PTZ (marker on time channel). The muscle artifact from the initial myoclonic twitch is seen immediately after the injection, followed by desynchronization of the EEG. The second segment shows the appearance of paroxysms, which was followed (third segment) by 5-6 Hz bursts of spike-and-wave complexes. Note the increased frequency of appearance of the spike-and-wave complexes with time.

B. Response to 15 mg/kg IV PTZ (marker on time channel) (p. 58). The initial desynchronization is followed by high voltage (300-600 μV) fast waves (20 Hz) coinciding with the initiation of a tonic convulsion. The second set of tracings shows the slower (down to 2 Hz) high voltage spikes corresponding to clonic convulsions. Abbreviations for the leads in this and subsequent figures are: LAC: left anterior cortex; RAC: right anterior cortex; LPC: left posterior cortex; RPC: right posterior cortex; BOA: basal olfactory area; LN: lenticular nucleus; HPC: hippocampus; THAL: thalamus; RF: reticular formation.

FIGURE 5A. PTZ SEIZURE 10 mg/kg IV

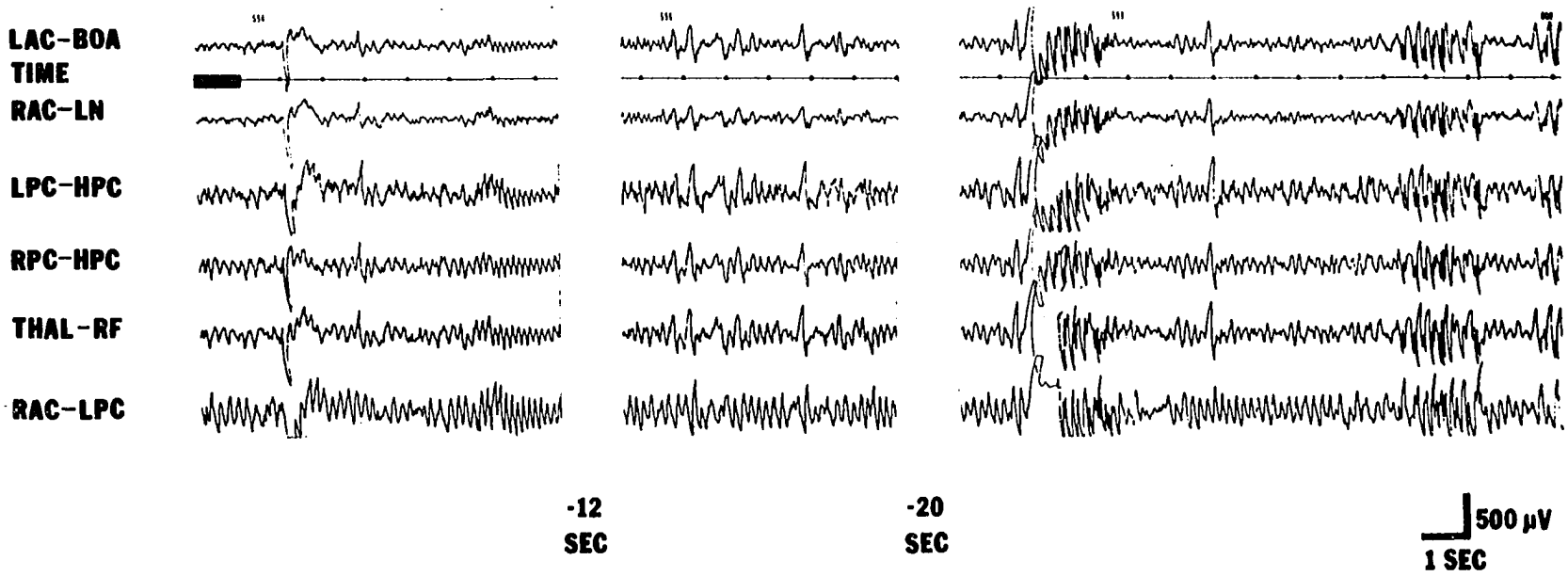


FIGURE 5B. PTZ SEIZURE 15 mg/kg IV

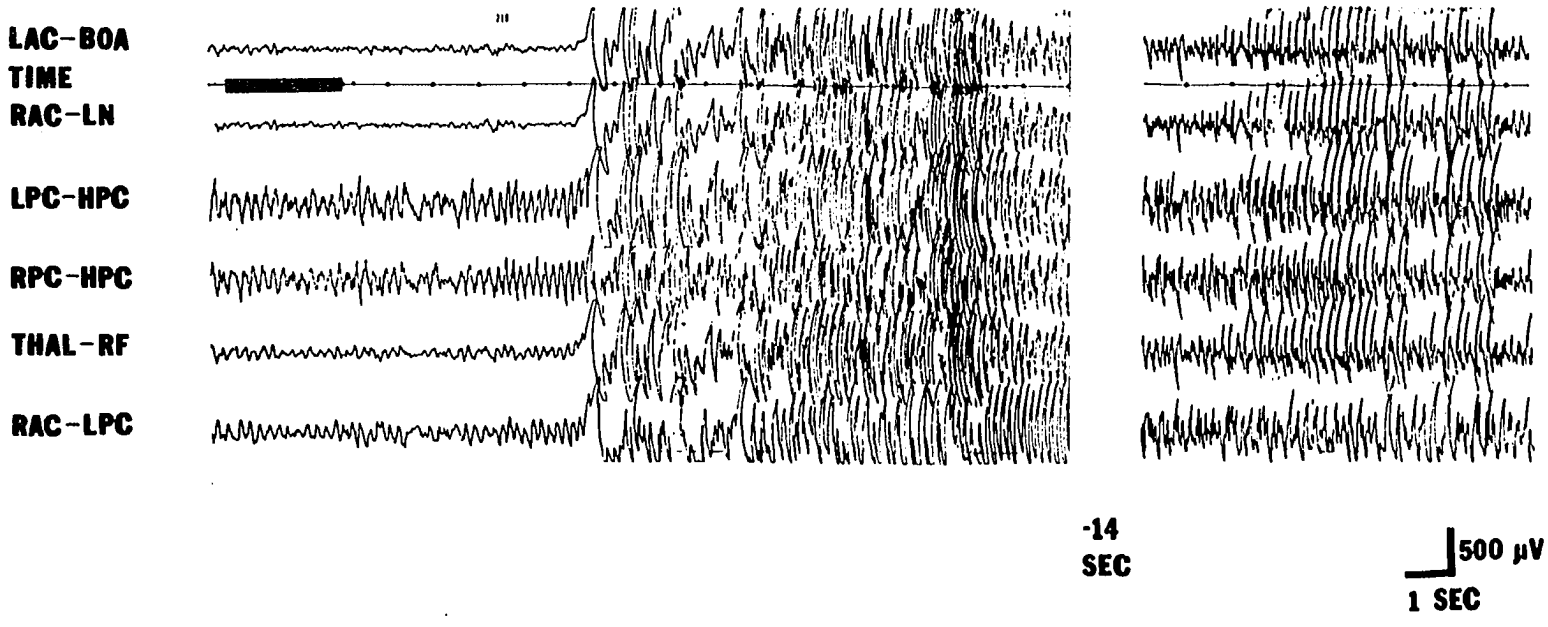


Figure 5. (Continued)

tion (Longo, 1962). Doses of 20 mg/kg resulted in grand-mal seizures of longer duration than those seen at 15 mg/kg.

The EEG tracings accompanying an electrically-induced seizure are shown in Figure 6. Adequate stimuli for induction of a generalized, 20-60 second myoclonic seizure were found to be 50 Hz, 1 msec pulse duration, 2 second train duration, and 4.0-7.6 volts. Lower stimulus voltages produced responses varying from slow waves (1-2 Hz) to short duration myoclonic seizures. The control stimulus intensity for a given rabbit could elicit seizures of comparable duration over a period of several hours, provided that thirty minute recovery periods between seizures were observed.

Biphasic cerebellar stimulation initiated 15-30 seconds prior to injection of the PTZ blocked the ictal activity or reduced the duration and amplitude of spikes, depending on the PTZ dose. The effects on seizure activity of changing the parameters of cerebellar stimulation were studied. Biphasic cerebellar stimulation (10 Hz, 1.5 msec, 4.0 volts), initiated 15 seconds prior to PTZ (15 mg/kg IV), prevented epileptiform activity, with the exception of an initial myoclonic twitch. Interruption of the cerebellar stimulation resulted in diffuse 3-4 Hz spikes after a 0.3-3.6 second delay (mean: 1.3±1.0 sec), while resumption of stimulation again antagonized the spiking (Figure 7). This was repeatedly demonstrated in this animal.

The cerebellar stimulation parameters of frequency, pulse duration and voltage were examined by holding two constant and varying the third. These variations are tabulated in Appendix B. Variations in the frequency

Figure 6. Electroencephalographic record of a seizure induced by electrical stimulation of the frontal cerebral cortex. Note the EEG desynchronization and appearance of spikes in the first segment which coincided with the beginning of the myoclonic convulsion. The second set of tracings shows the fully-developed seizure, and the third set shows the termination of the seizure. Stimulus parameters: 5 volts, 50 Hz, 1 msec pulse duration, 2 second train duration. Arrows: stimulation on (up) and stimulation off (down).

FIGURE 6. ELECTRICALLY-INDUCED SEIZURE

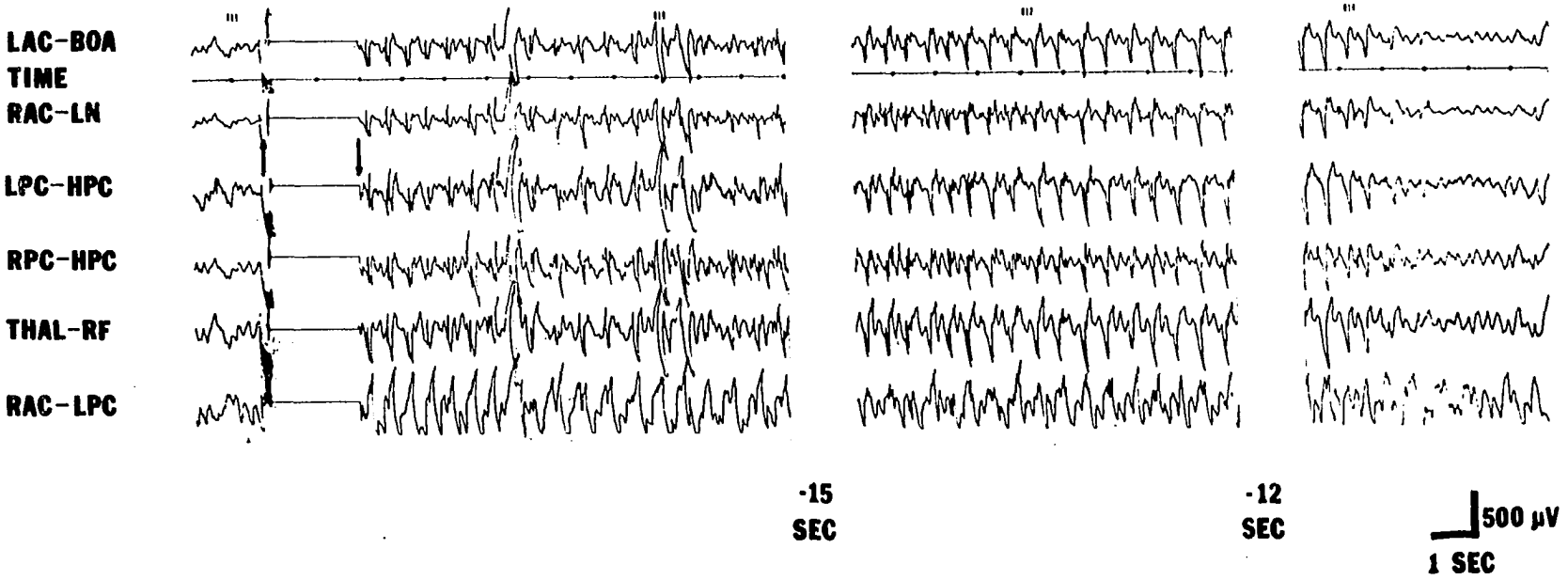
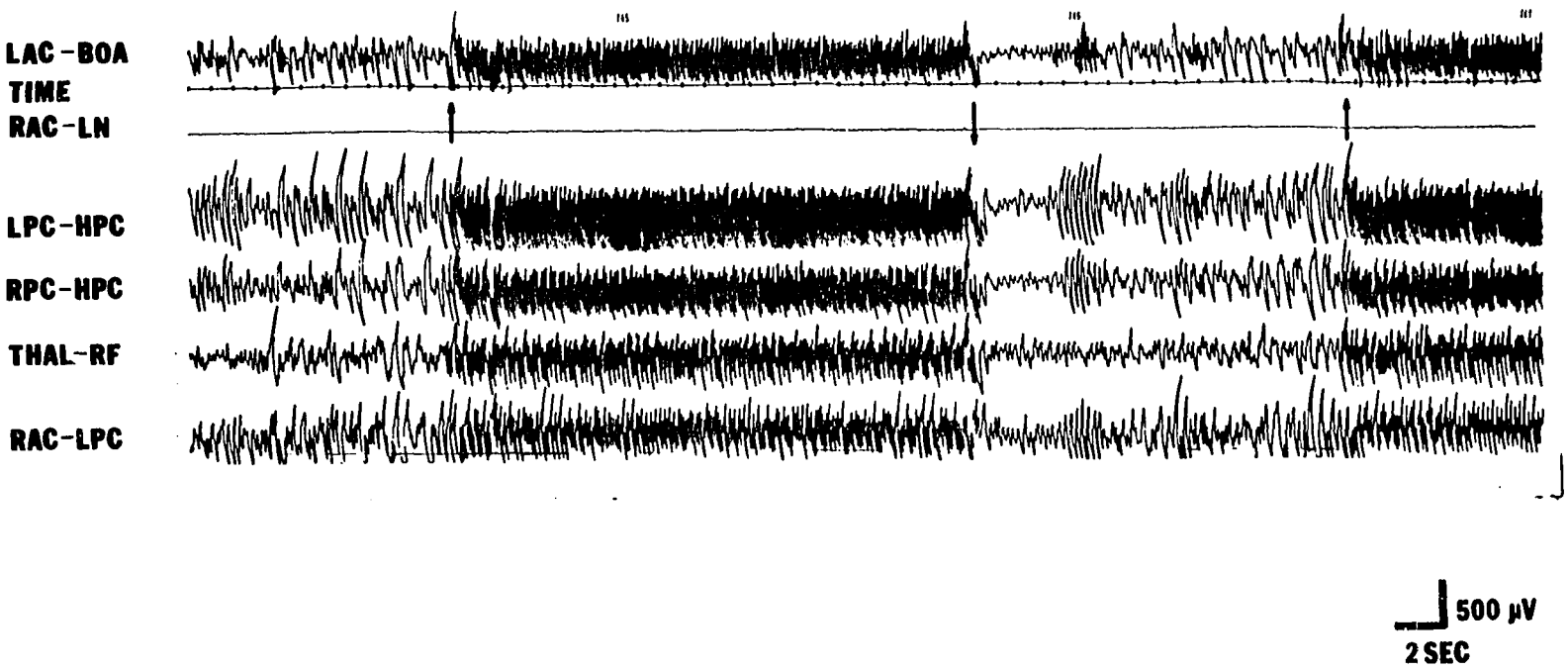


Figure 7. Block of PTZ (15 mg/kg IV) seizure activity by cerebellar stimulation. PTZ had been administered approximately three minutes earlier. Note delay in reappearance of spikes after cerebellar stimulation is terminated (down arrow). Stimulus parameters: 4 volts, 10 Hz, 1.5 msec. RAC-LN recording absent due to electrode failure. Arrows: stimulation on (up) and stimulation off (down).

FIGURE 7. CEREBELLAR STIMULATION BLOCK OF SEIZURE ACTIVITY



revealed that 10 Hz was most effective in suppressing spikes, 8 or 12 Hz was less effective, and 6 Hz was ineffective. Duration variations showed 1.5-2.0 msec to be effective, 1.0 msec less effective and 0.15 msec ineffective. Ineffective stimulus parameters resulted in bursts of spikes superimposed on the stimulus artifact. The voltage necessary to prevent epileptiform activity varied from animal to animal, and for any dose of PTZ the required voltage level decreased with time after the injection. At the time of PTZ injection (15 mg/kg) in the above-mentioned experiment, a 4.0 volt stimulus was adequate to antagonize the seizure, while a stimulus of 3.0 volts or less was insufficient. Four minutes after injection, 3.6 volts suppressed the spikes and bursts of spikes, while 3.4 volts did not. Twelve minutes after injection, 2.6 volts was effective while 2.2 volts was not. In all instances where inhibition of EEG seizure activity was observed, intensities of 3-4 volts were adequate to produce the inhibition. A frequency of 10 Hz and pulse durations of 1.0-1.5 msec were routinely applied.

Cerebellar stimulation at 10 Hz inconsistently reduced electrically-induced seizure activity, and 100 Hz stimuli yielded no effect. On three or four occasions seizures were blocked, delayed in onset, or reduced in duration or amplitude. However, on a similar number of occasions, attempts to induce seizures at 4-7 volts also failed to elicit a seizure, even in the absence of anticonvulsants. These effects were not consistent in the same animal or from animal to animal.

Comparisons were made between seizures obtained during the control period and seizures obtained after the anticonvulsant treatment. Data

measurements of the elevation of EEG seizure thresholds are compiled in Table 3. Dose or voltage levels measured during the control period, and after presentation of the anticonvulsant treatment are entered as well. Also included is the elevation of seizure threshold (ΔT), defined as the difference between the elevated and control levels, and the statistical significance of ΔT. The units for electrical and PTZ seizures differed (volts or mg/kg), so ΔT is also expressed as a percentage of the control level ($\Delta\%$) to permit comparisons of the elevations of seizure thresholds by different treatments. For each block of data the estimates of the mean ($\bar{X}$) and standard deviation (s) of ΔT and $\Delta\%$ are calculated. The statistical analyses of the six combinations of the four blocks of data from Table 3 are summarized in Table 4. Elevation of PTZ seizure thresholds by phenobarbital was significantly greater than elevation by cerebellar stimulation, and elevation of PTZ seizure thresholds by phenobarbital was significantly greater than elevation of the threshold for electrical seizures by DPH ($p<0.05$). The other four comparisons showed no significant differences. None of the comparisons showed a difference between treatments at the 0.01 level.

Cerebellar stimulation failed to block electrically-induced seizures in ten rabbits in a second series of investigations (see above). In a final group of three consecutive experiments, seizures elicited by the administration of PTZ (15 mg/kg) were blocked with cerebellar stimulation while electrically-induced seizures were unaffected. In two experiments, phenobarbital (25 mg/kg IV) was administered, and stimulation at the seizure voltage was repeated.

Table 3. Elevations of seizure thresholds

Seizure/treatment	Animal number	Control[a]	Elevated[a]	ΔT[b]	$\Delta\%$[c]	Significance level
PTZ/phenobarbital (N=6)	50	10	19	9	90	
	51	10	18	8	80	
	52	15	20	5	33	
	53	10	16	6	60	
	54	10	18	8	80	
	56	5	13	8	160	
				$\bar{X}$=7.33	$\bar{X}$=83.83	
				s=1.51	s=42.48	p<0.005
Electrical/ phenobarbital (N=5)	58	5.0	9.0	4.0	80	
	59	4.0	5.6	1.6	40	
	60	5.6	6.7	1.1	20	
	61	7.0	13.0	6.0	86	
	62	5.0	6.0	1.0	20	
				$\bar{X}$=2.74	$\bar{X}$=49.20	
				s=2.19	s=31.99	p<0.025

[a] Units of mg/kg for PTZ seizures and volts for electrical seizures.

[b] ΔT = elevated value minus control value, mg/kg or volts.

[c] $\Delta\%$ = change in percent.

Table 3. (Continued)

Seizure/treatment	Animal number	Control	Elevated	ΔT	Δ%	Significance level
Electrical/DPH	63	6.0	9.8	3.8	63	
(N=5)	65	5.4	7.2	1.8	33	
	66	5.4	7.4	2.0	37	
	67	6.4	7.5	1.1	17	
	68	7.6	8.9	1.3	17	
				$\bar{X}$=2.00	$\bar{X}$=33.40	
				s=1.07	s=18.89	p<0.01
PTZ/cerebellar	77	5	7	2	40	
stimulation	78	15	24	9	60	
(N=6)	79	10	13	3	30	
	80	15	18	3	20	
	81	10	14	4	40	
	83	15	17	2	13	
				$\bar{X}$=3.83	$\bar{X}$=33.83	
				s=2.64	s=16.74	p<0.01

Table 4. Statistical comparison of elevations of seizure thresholds

Seizure/treatment comparison[a]	Null hypothesis (H_o)	Alternative hypothesis (H_1)	Degrees of freedom	T' value	$p<0.05$	$p<0.01$
PTZ/PHE vs. ELEC/PHE	$\mu_1 = \mu_2$	$\mu_1 > \mu_2$	8	1.540	+[b]	+
PTZ/PHE vs. ELEC/DPH	$\mu_1 = \mu_2$	$\mu_1 > \mu_2$	7	2.614	-	+
PTZ/PHE vs. PTZ/CBL	$\mu_1 = \mu_2$	$\mu_1 > \mu_2$	6	2.682	-	+
ELEC/PHE vs. ELEC/DPH	$\mu_1 = \mu_2$	$\mu_1 > \mu_2$	6	0.951	+	+
ELEC/PHE vs. PTZ/CBL	$\mu_1 = \mu_2$	$\mu_1 > \mu_2$	5	0.969	+	+
ELEC/DPH vs. PTZ/CBL	$\mu_1 = \mu_2$	$\mu_2 > \mu_1$	8	0.040	+	+

[a]PTZ = pentylenetetrazol seizure, ELEC = electrically-induced seizure, PHE = phenobarbital, DPH = diphenylhydantoin, CBL = cerebellar stimulation.

[b]+: accept the null hypothesis; -: reject the null hypothesis.

In both experiments the electrical seizure activity was blocked by the phenobarbital. In one experiment PTZ effects were also antagonized by the phenobarbital. Thus it was possible to demonstrate electrical and chemical block of chemical seizures, and chemical block of electrical seizures, but not electrical block of electrical seizures. These results are summarized in Table 5.

Table 5. Summary of anticonvulsant treatment effects on PTZ and electrically-induced seizures

	Anticonvulsant treatment effect[a]		
Seizure model	DPH	Phenobarbital	Cerebellar stimulation
PTZ	-	+	+
Electrical	+	+	-

[a]+: antagonism of seizure activity; -: no effect on seizure activity.

Cerebellar stimulation changed the patterns of PTZ seizure activity in addition to elevation of the seizure thresholds. With increases of pentylenetretrazol dose from 10 to a maximum of 24 mg/kg in increments of 2 or 3 mg/kg (Table 3), a variable electrographic pattern was observed. Ten to twenty seconds after injection, a burst of 5-8 seconds of diffuse high amplitude (400-500 μV), high frequency (8-15 Hz) spikes were seen (initial spiking), followed by approximately sixty seconds of bursts of high amplitude (300-600 μV) spikes at 1-2 Hz (secondary spiking). As the dose was increased within the range stated above, the frequency of the

initial spiking increased to 20 Hz or greater, the low frequency spike pattern changed from bursts to continuous, and spike amplitudes increased to 500-600 μV. At higher dose levels in some animals the initial burst duration increased until it approximated the seizure seen with a 15 mg/kg PTZ dose without cerebellar stimulation. With other preparations the initial burst remained unchanged with increasing PTZ doses while the secondary spiking increased in duration, frequency and amplitude until the control seizure was approximated. Figure 8 displays a seizure elevation pattern of the latter type. Tracing A shows the EEG after a 15 mg/kg dose of PTZ, while tracing B shows the EEG of the same rabbit after a 16 mg/kg dose of PTZ with the concurrent application of cerebellar stimulation. Finally, in two animals the durations of both the initial burst and the secondary spiking did not show an increase, but the frequency and amplitude increased in severity, and a post ictal depression occurred after the period of low frequency spikes. At the highest dose levels the EEG became isoelectric and death ensued.

These results differed from those seen with phenobarbital-induced elevation of PTZ seizure thresholds, where higher dose levels were required to evoke the patterns usually seen with 10 and 15 mg/kg PTZ doses. Pattern changes observed in the presence of phenobarbital other than the elevations of threshold were minimal. The only prominent effect is shown in Figure 9, where the responses to 10 mg/kg PTZ doses are graphed. The times from injection of PTZ until the first and second paroxysms for both the 10 mg/kg control seizure and the 10 mg/kg seizure in the presence of phenobarbital were averaged for the first six experiments of Table 3. The

Figure 8. Effect of cerebellar stimulation on the electrographic responses to intravenous injections of PTZ (marker on time channel).

A. PTZ, 15 mg/kg IV. Compare with the response shown in Figure 5B. (Note difference in time scales.)

B. Effect of cerebellar stimulation (10 Hz, 3 volts, 1.5 msec) on the electrographic response to PTZ, 16 mg/kg IV (p. 73). The threshold elevation pattern can be seen to appear as a brief high frequency (8 Hz) burst fourteen seconds after the start of injection (arrow), followed by occasional spikes at 2 Hz frequency. Tracings taken from same animal as Figure 8A.

FIGURE 8A. PTZ 15 mg/kg WITHOUT CEREBELLAR STIMULATION

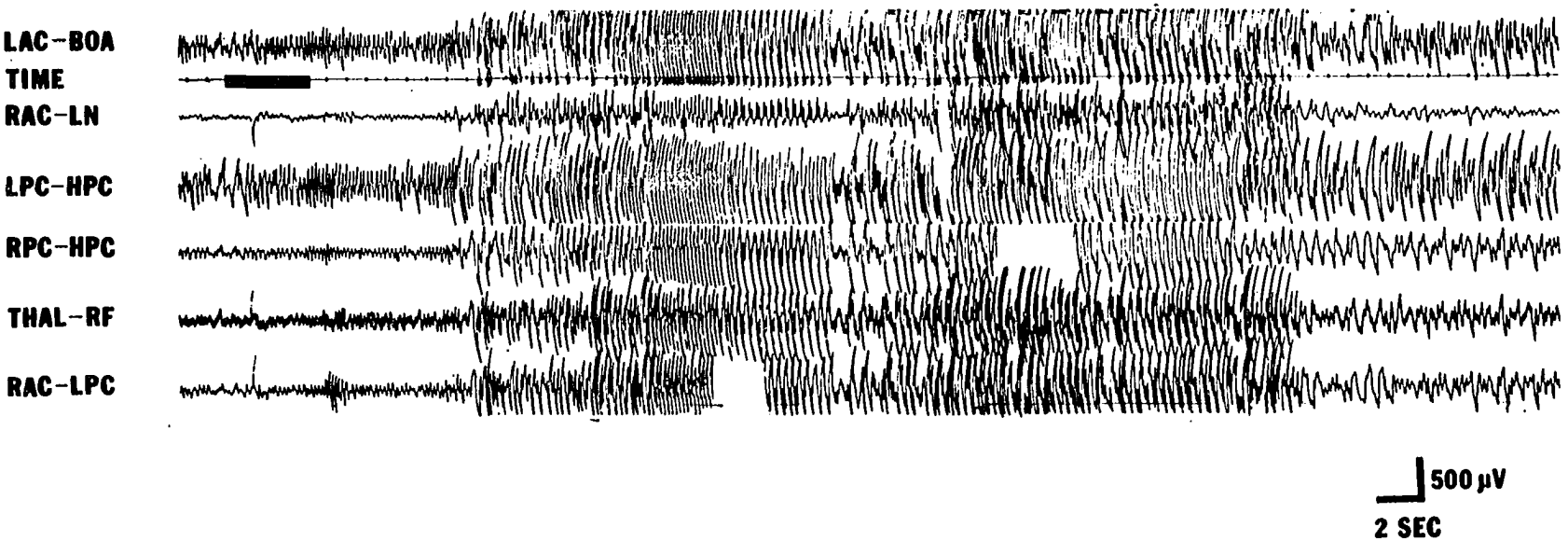


FIGURE 8B. PTZ 16 mg/kg WITH CEREBELLAR STIMULATION

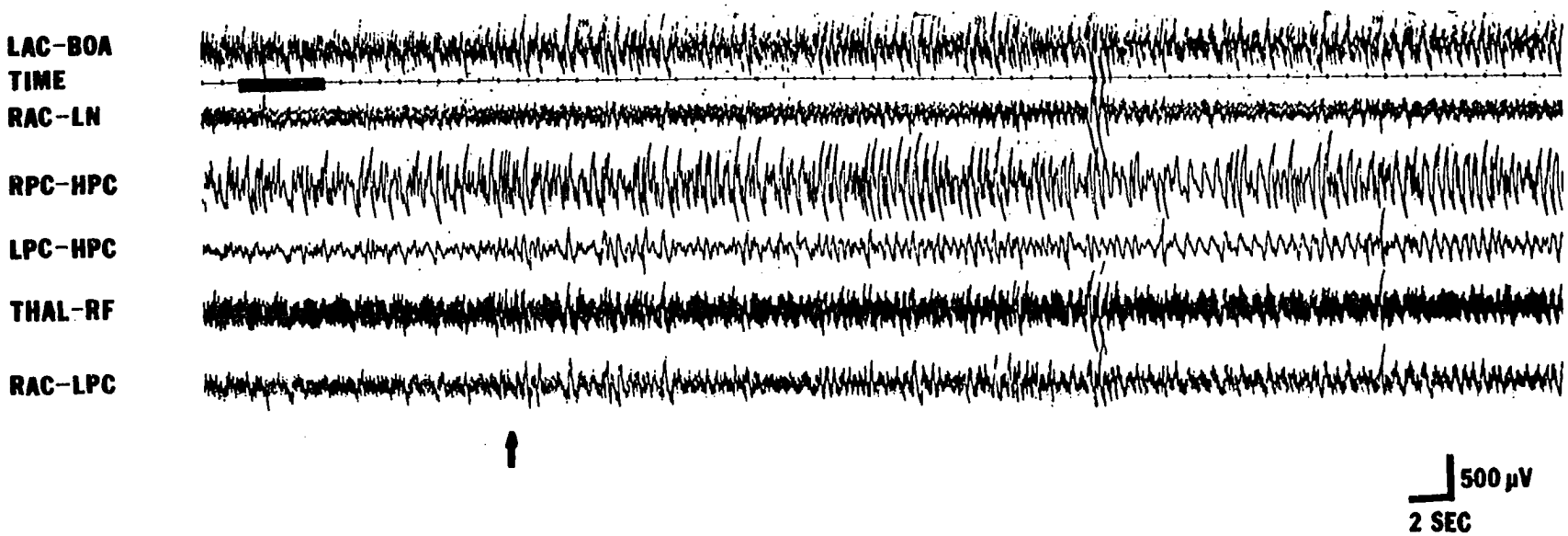
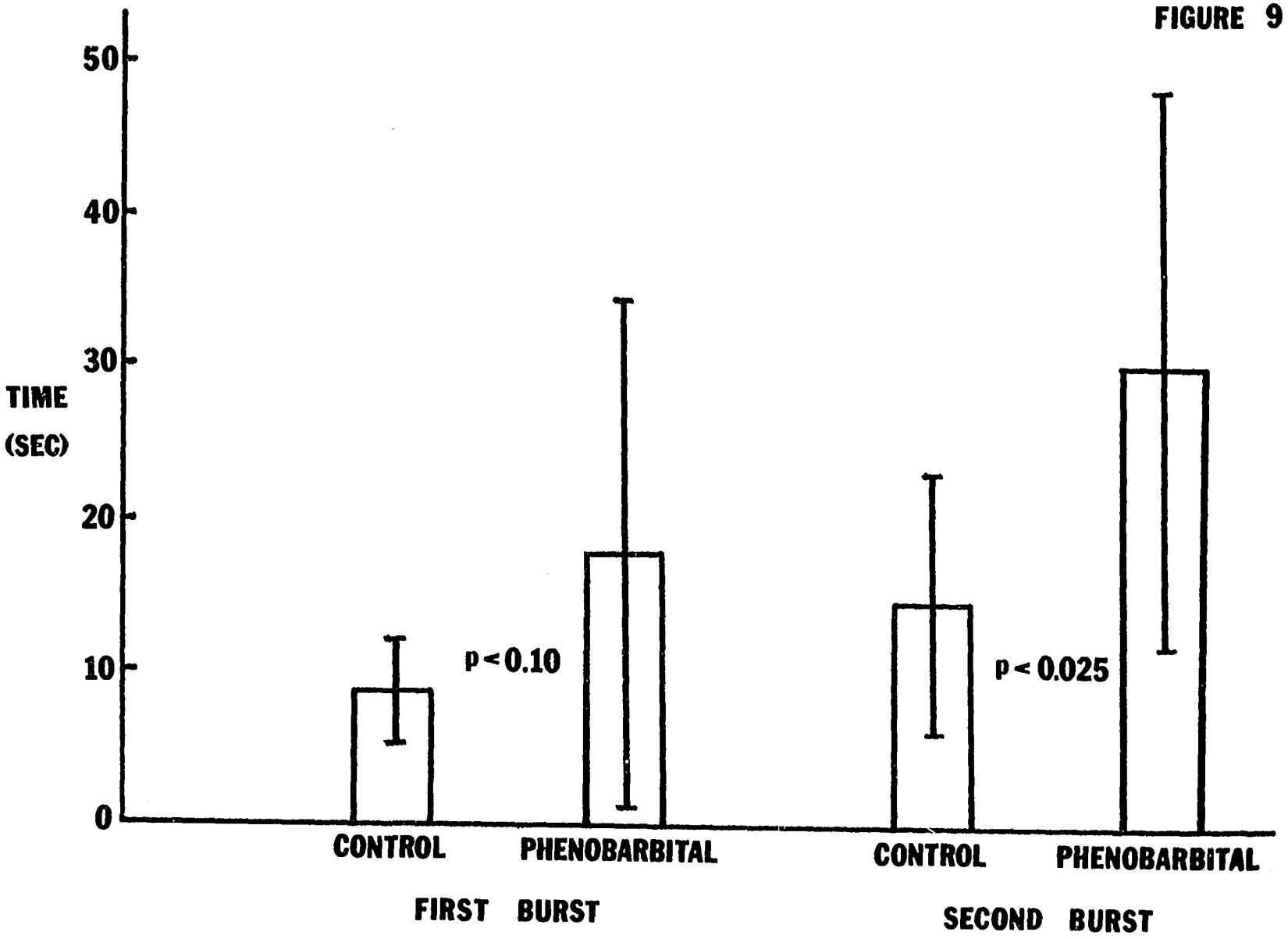


Figure 8. (Continued)

Figure 9. Averaged delay in response to the first and second paroxysmal bursts in the EEG after PTZ injection (10 mg/kg IV), with and without phenobarbital (25 mg/kg IV). The times to the first and second bursts with phenobarbital were greater than the times for the control seizure at the 0.10 and 0.025 levels of significance, respectively. Standard deviations are represented by the vertical bars.

FIGURE 9


50
40
30
20
10
0
TIME
(SEC)
p < 0.10
p < 0.025
CONTROL
PHENOBARBITAL
CONTROL
PHENOBARBITAL
FIRST BURST
SECOND BURST

average time to the first paroxysm with phenobarbital was greater than the time seen during the control seizure at the 0.10 level of significance, while the time to the second burst with phenobarbital was greater at the 0.025 level. Thus the delaying effect of phenobarbital on PTZ paroxysms was significant for the second burst only.

When electrically-induced seizures were antagonized with the anticonvulsant drugs phenobarbital and diphenylhydantoin, seizure patterns were largely unchanged. However, the increases in seizure amplitude and duration with increases in stimulation voltage were not synchronized: Spike amplitudes matched and then surpassed the spike amplitudes seen during the control period before the seizure durations matched those of the control period. The effects of these drugs on electrically-induced seizure durations are graphed in Figure 10. Average seizure durations after the control voltage and after the control voltage with DPH or phenobarbital were both significantly different at the 0.005 level.

Electrically-induced seizures challenged with cerebellar stimulation showed no consistent changes in the seizure patterns. While cerebellar stimulation had no effect on seizure duration, a delay in seizure onset and a reduction in spike amplitudes was occasionally observed if the cerebellar stimulation was applied before seizure induction. However, a more frequent effect of cerebellar stimulation on electrically-induced seizures was an extension and intensification of seizure activity. Neither response was consistently obtainable, and the most common response was no effect.

Figure 10. Effects of phenobarbital (25 mg/kg IV) and DPH (30 mg/kg IV) on durations of electrically-induced seizures. Mean durations of seizures with phenobarbital or DPH were significantly different at the 0.005 level when compared to control. Standard deviations are represented by the vertical bars.

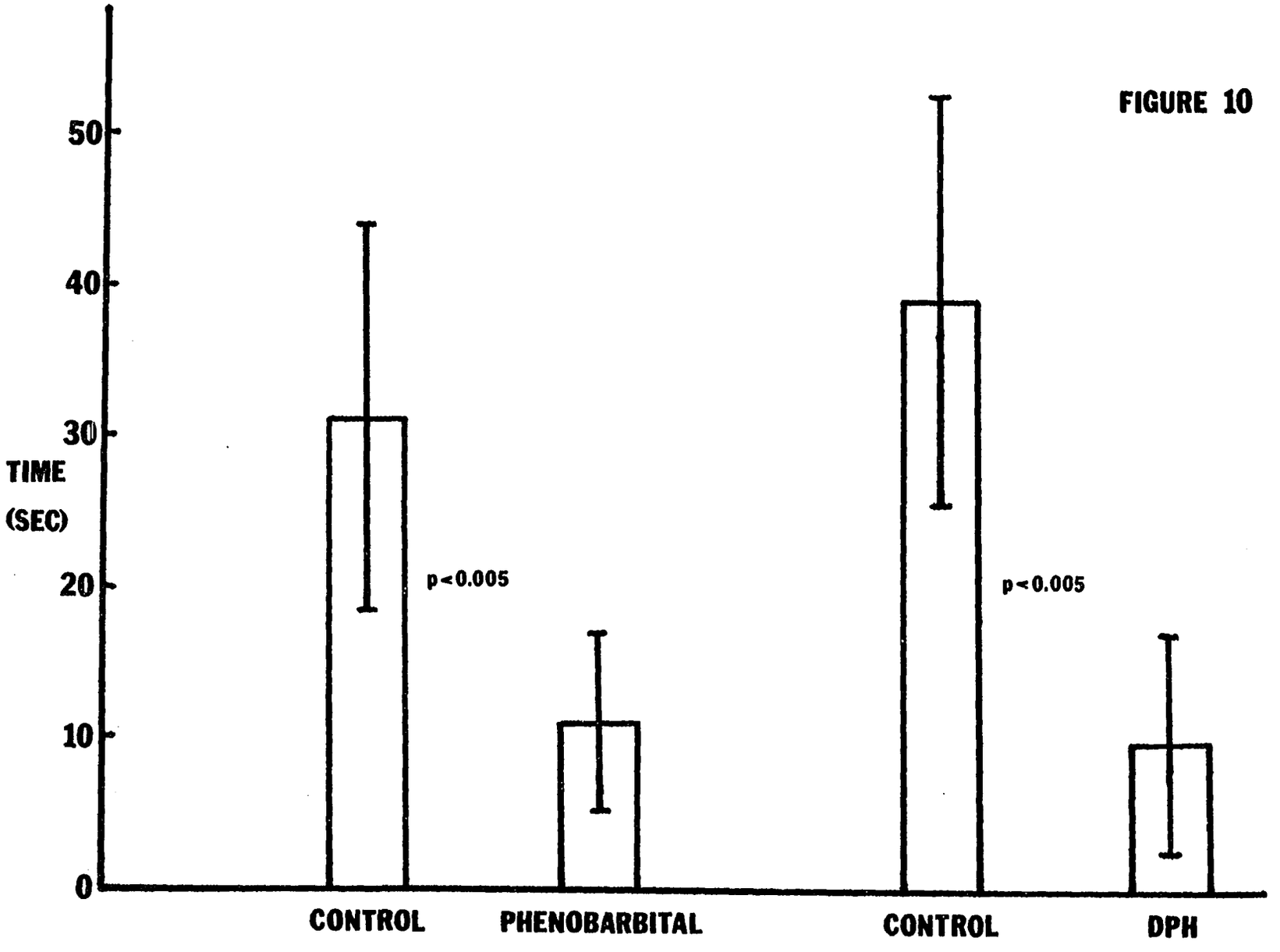

50
40
30
TIME
(SEC)
20
10
0
p<0.005
p<0.005
CONTROL
PHENOBARBITAL
CONTROL
DPH

FIGURE 10

DISCUSSION

The primary question considered in this investigation concerns the relative efficacies of cerebellar stimulation, DPH, and phenobarbital as anticonvulsant treatments. The other extant study of this topic considered a highly dissimilar experimental paradigm and reported conflicting results. In the present research, seizures were induced in acute, unanesthesized rabbits with intravenous PTZ or electrical stimulation of the frontal cerebral cortex. Elevations of seizure thresholds by treatment with intravenous DPH or phenobarbital, or with cerebellar stimulation were not statistically different at the 0.01 level of significance. Two exceptions were: (1) DPH did not block PTZ seizures, and (2) cerebellar stimulation did not block electrically-induced seizures. Englander et al. (1975) and Johnson et al. (1976) examined the excitability of the thalamocortical motor (TCM) system in acute, anesthetized cats. Cerebral cortical potentials evoked by pairs of electrical pulses delivered to the ventrolateral thalamus were suppressed by cerebellar stimulation or a variety of anticonvulsant drugs, including DPH but not phenobarbital. In contrast to the results of the present research, cerebellar stimulation was markedly superior, completely suppressing the evoked response, while DPH only produced a 48% reduction in amplitude. Several differences between the studies, discussed below, indicate that the results of the present research may provide a more accurate assessment of relative treatment efficacies.

The experimental designs of these two studies differed most significantly in the electrophysiological activity considered, seizure activity

or TCM system excitability. Measurement of the excitability of the TCM system provides an indication of the electrical excitability of the thalamus and cerebral cortex and the functional patency of the thalamocortical projections. Johnson et al. (1975) noted a reduction in the width and amplitude of the TCM system excitability curve coincident with a decrease in chloralose spikes in the EEG, and then (Johnson et al., 1976) looked for a similar effect on the excitability curve from anticonvulsant treatments, with the implication that a decrease in TCM system excitability correlated with anticonvulsant activity. The thalamus and cerebrum are involved in most seizure activity, and both thalamic and midbrain structures appear to be associated with maintenance, spread and inhibition of seizure activity (Goldensohn and Ward, 1975). In addition, an increase in the excitability of the TCM system may accompany seizure activity, just as a decrease accompanied the cessation of chloralose spikes. However, caution must be exercised in ascribing a direct relationship between effects on the TCM system and effects on seizure activity, particularly since thalamocortical pathways have not been implicated as pathways whereby cerebellar stimulation inhibits seizure activity.

One difference between the two studies which makes interpretation and comparison difficult is the use of anesthetic (chloralose or pentobarbital) in the TCM system study. Since general anesthesia significantly affects all areas of the nervous system, with different areas often affected unequally, interpretation of data obtained under these conditions and application of it to conscious animal preparations are difficult. A study of the effects of anticonvulsants on the TCM system without general anesthesia might produce contrastive results.

The cerebellar electrode placement used in the TCM system study did not differ greatly from that used in the present research (paramedian vs. ansiform and simplex lobes), but the stimuli were applied unilaterally rather than transhemispherally, and shifts in placement as small as 1-2 mm abolished the observed effects. Further, pulse durations did not differ (1 msec), but waveform and frequency did. Unidirectional pulses were used, and the above-described results were only obtainable at a frequency of 100 Hz. Cerebellar stimuli at 10 Hz only occasionally reduced the duration of the excitability curve and had no effect on its amplitude.

Finally, differences in the drug regimens utilized in the two studies are noteworthy. Total DPH doses of 80 mg/kg were injected for the TCM system study, a level significantly greater than the 30 mg/kg used in this research. In addition, determinations of the excitability curves were not made until peak effects of the drug had been obtained, while standard delays of thirty minutes were observed in this investigation. Higher doses and peak effects would be expected to increase the efficacy of DPH in comparison with cerebellar stimulation; however, when compared with the results of the present research, an opposing result was observed.

In light of the differences in experimental design and results noted above, the effects of anticonvulsant treatments observed with the TCM system cannot be taken as indicative of relative effects on induced seizure activity. Rather, TCM system effects produced by the anticonvulsant treatments were concomitant to and separate from effects on seizure activity. While the TCM system may become useful for determining the presence or absence of anticonvulsant activity associated with a given compound,

direct observation of the effects of anticonvulsants on seizure activity would appear to be a more accurate index of relative anticonvulsant activity. The results of this portion of the present research provide the only quantification of the relative anticonvulsant efficacies of cerebellar stimulation and anticonvulsant drugs to date. Although the results are based on acute stimulation or drug administration challenging induced seizures in rabbits, information of this nature will be required to justify the use of cerebellar stimulation as a standard therapeutic adjunct for the treatment of epilepsy. This justification will be necessary for both the neurologist or neurosurgeon treating a specific epileptic patient and the federal agencies responsible for authorizing the unrestricted use of new therapies.

The second subject of this investigation was parameters of cerebellar stimulation. The stimulation parameters developed by Cooper (1973) for human use (7-15 Hz, 1 msec, 5-14 volts) were chosen for initial evaluation because of their demonstrated clinical efficacy. The cerebellar stimulating electrodes initially employed in this study consisted of silver ball electrodes without the barrel and hub assembly, cemented to the skull with denture acrylic. Stimulation produced contraction of ear and facial muscles at 10 Hz, indicating activation of brain stem structures; post-mortem examination revealed that the electrodes had been inserted to depths near the cerebellar nuclei and peduncles. Stimulation at this depth had no observable effect on seizure activity. This observation is of interest in light of the criticism of early investigations that the effects attributed to cerebellar stimulation were in fact due to current

spread to the brain stem. Subsequently, cerebellar stimulating electrodes were mounted in barrel and hub assemblies to insure cortical placement.

The effective values established in this study were quite narrow: Respective changes of 4 Hz, 1.35 msec, or 1 volt in frequency, pulse duration, or amplitude were adequate to terminate the blocking effect of cerebellar stimulation. While the specific values found are in line with other published accounts (cf. Figure 4), the high degree of specificity of stimulation parameters has not been reported previously. A narrow range of pulse durations (1-2 msec) has been consistently utilized in the studies reporting suppression of seizure activity, but wide deviations in frequency and amplitude have been successfully used from study to study and within the same study. While large variations in amplitude may be ascribed to differences in impedance or the use of suprathreshold stimulation, the variation in effective frequencies is not easily explained. In particular, effective frequencies in the range of 100-200 Hz have been reported at least as often as those near 10 Hz. One explanation for this discrepancy may be suggested by observations made by Cooper et al. (1976a,b). A general, but not absolute, observation with their clinical investigations has been that low frequency (10 Hz) stimulation is most effective with seizure disorders, while high frequency (100-200 Hz) stimulation is most effective with spastic muscle disorders. A possibility exists that the several neurophysiological disfunctions affected by cerebellar stimulation respond selectively to either high or low frequency stimulation because of differences in the physiological mechanisms and neural structures involved. This could explain the frequency-dependent

effects of cerebellar stimulation on decerebrate rigidity observed by Moruzzi (1948a-d). Similarly, differing seizure states and models may respond to different frequency ranges because of differences in the physiological mechanisms and neural structures involved in initiating and sustaining the seizure activity. An additional difference which might be accountable is anatomical species variation. Gilman et al. (1976) suggested that the results and postulated mechanisms and pathways for effect from earlier investigations were of questionable applicability to human studies since the experiments were performed on cats, a species in which the cerebellar efferents differ significantly from man.

While the parameter study of this investigation is based on one rabbit, the values found were effective for all subsequent tests with PTZ. A frequency of 100 Hz was tested when attempting to block electrically-induced seizures, but because of the observed intractability of the electroconvulsive model, no conclusion on the efficacy of this frequency could be made. PTZ seizures were not tested with 100 Hz cerebellar stimuli.

A number of investigations of the effects of cerebellar stimulation reported negative results when attempting to block seizure activity (see Literature Review). Since all of these studies utilized parameters significantly different from at least one of the ranges determined in the present study, the failures may be partially attributable to use of ineffective stimulus parameters.

The cerebellar stimulation in this study was applied on an acute basis. However, evidence from a number of experimental and clinical

investigations indicates that the therapeutic efficacy of electrical stimulation of neural tissue may be contingent on chronicity of application. In addition to the above mentioned delayed responses to cerebellar stimulation for seizures observed by Cooper et al. (1974) and Babb et al. (1975), Sweet (1975) observed delays of three weeks in several patients when using electrical stimulation of the dorsal columns of the spinal cord for pain control, and Cooper et al. (1976b) found continued improvement over five month periods when using cerebellar stimulation to treat cerebral palsy. Further, Black et al. (1976) were unable to affect alumina- or electrically-induced focal seizures with cerebellar stimulation on an acute basis in monkeys, but found a significant reduction in the alumina seizure frequency when the stimulation was applied chronically. (No report was made of chronic stimulation with electrically-induced seizures.) It is therefore possible that certain seizure models, seizure models in certain species, or certain seizure models in certain species are unaffected or only weakly affected by cerebellar stimulation unless it is applied on a chronic basis. This effect might explain the intractability of electrically-induced seizures in the present research. Although cerebellar stimulation has been found effective on an acute basis in numerous studies, it is also possible that the same parameters applied on a chronic basis would be even more potent. Conversely, further investigation may show that while some seizure models require chronic stimulation, others display no improvement in response with time.

The seizure activity studied in this investigation was induced by two methods, intravenous injection of the systemic convulsant PTZ, and cere-

bral cortical electroshock. Because of the diverse neuropathies collected under the heading of epilepsy, no one model of seizure activity is a good representation of that collective disease state. However, sufficient experimental models of epilepsy have been developed (Purpura et al., 1972) which closely replicate specific human seizure types, or specific aspects of a seizure type, to insure that a good system is usually available for investigating an area of specific research interest. Most experimental investigations of cerebellar stimulation in the past have employed models of focal seizure activity (topical cobalt, alumina, penicillin, or electrical stimulation); however, clinical studies have centered on epileptics with generalized or psychomotor seizure states. Of these two, models of generalized seizure states are more easily established, most often with electroshock or systemic convulsants. Several features of both PTZ and electroshock seizures make them advantageous for comparative studies. Since the seizures are individually induced rather than being spontaneous, elaborate monitoring systems or long periods of observation are not required for quantifying seizure activity and anticonvulsant effects. Variations of dose or stimulus intensity permit control of the seizure severity, so that a standard seizure can be established, both within a single animal experiment and from animal to animal. Further, the inherent repeatability of the seizures permits a more precise and reliable experimental design.

PTZ seizures are probably the best model of generalized seizures as seen in man. Gastaut and Fischer-Williams concluded that ". . . pentylenetetrazol-induced seizures are the only ones which faithfully reproduce

spontaneous epilepsy in man with its hypersynchronous cortical discharge and its well-differentiated tonic and clonic phases" (Gastaut and Fischer-Williams, 1959, p. 341). Although PTZ and electrically-induced seizures are routinely used for testing potential anticonvulsant drugs (Mitchell and Keasling, 1960), the electroconvulsive model is not as close an approximation of seizures in man (Black et al., 1976).

Several aspects of the PTZ and electroconvulsive models detract from their suitability for this study. Because of rapid metabolism and elimination of PTZ, convulsive doses can be administered repeatedly during the course of an experiment (Ayala et al., 1961). Nonetheless, the elimination of PTZ was not completed within the thirty minute recovery periods observed between seizures. Esplin and Woodbury (1956) demonstrated that the elimination of a 30 mg/kg subcutaneous PTZ dose was not completed until 48 hours after injection. Thus repeated seizure induction with PTZ resulted in a progressive accumulation of the drug in the blood, reducing the accuracy of measurements of seizure threshold elevations. However, since the same effect was encountered with all three PTZ-anticonvulsant interactions, the relative efficacies remained essentially unchanged.

A second problem inherent in PTZ use is created by its route of administration. Since the seizures are induced by a chemical in the bloodstream, they cannot be terminated abruptly: The chemical irritation of the nervous system is continually being applied as long as sufficient quantities remain. Therefore a brief train of cerebellar stimuli is not adequate to block a PTZ seizure, although it is sufficient for epileptic seizures in humans and electrically-induced seizures in some animals.

These decrementing blood levels of PTZ would account for the observed decrease in requisite stimulus intensity with time, and the off and on block of seizure activity shown in Figure 7.

A further complication occurring with the repeated induction of seizures, both PTZ and electrically-induced, is a progressive exhaustion of the animal due to the debilitating effects of the convulsions. The corporal aspect of the fatigue could be eliminated by paralysis and mechanical ventilation; however, the trachaeostomy would necessitate the use of a general anesthetic, which would in turn deleteriously affect the electroencephalographic data. The CNS fatigue could be reduced by longer recovery periods between seizures, but this would be impractical with acute experiments. Assessment of the magnitude of the effects of exhaustion and accumulated PTZ was not possible once the anticonvulsant drug had been administered, since the control seizure could not be rerun. However, in one PTZ-cerebellar stimulation experiment (rabbit #77), the control seizure (5 mg/kg PTZ) was increased in duration between 5 and 10% after ten PTZ injections in 5 1/2 hours, and the post ictal depression was more pronounced. No regular evaluation of this effect was made.

The most significant failing of these models was the observed intractability of the electroconvulsive model with respect to cerebellar stimulation. It is possible that chronic cerebellar stimulation could prove to be more effective, yet this may be questioned since Cooper and Snider (1974) were able to block electrically-induced focal seizures with cerebellar stimulation in acute rhesus monkeys. The difference might be due to species differences (see above, Gilman et al., 1976) or, more

likely, model differences, since they observed that ". . . it has not been possible to stop the seizure discharges when they have endured and become generalized" (Cooper and Snider, 1974, p. 254). Of the differences between reports citing success and failure in blocking seizure activity, including the present research, the most significant may be model differences. While the total mechanisms of both PTZ and electrically-induced seizures remain to be elucidated, there is no question that they differ. The cerebellum itself appears to play a role in initiating and/or sustaining electroshock seizures, since cerebellectomy in rats raised the threshold for electrically-induced seizures but did not affect the threshold for PTZ seizures (Raines and Anderson, 1976). Further experimentation will be necessary to determine whether chronic stimulation will affect electrically-induced generalized seizures in rabbits, or if they are absolutely intractable due to species differences or the electroconvulsive model itself.

Several questions have been raised by the results of this investigation and the problems observed with the use of the PTZ and electroconvulsive seizure models. Some of them could be resolved with the use of chronic animal preparations, both with and without chronic cerebellar stimulation. The problems of exhaustion and PTZ build up could be eliminated, and a more accurate assessment of the elevations of seizure thresholds by stimulation and anticonvulsant drugs would be possible. Since maximal anticonvulsant effects are obtained when a steady state blood level is achieved over a period of days or weeks, and cerebellar stimulation may prove to be more effective on a chronic basis, the rela-

tive efficacies of the drugs and stimulation may be observed to change. Both the control seizures and the measured elevations of seizure threshold could be examined for changes with time. Further, the residual suppressive effect of cerebellar stimulation seen when the stimulation is turned off (Figure 7) could be investigated. Finally, the question of whether cerebellar stimulation on a chronic basis would affect electrically-induced generalized seizures could be resolved.

A number of larger questions also remain to be resolved. The mechanisms whereby cerebellar stimulation suppresses seizure activity are not much better understood now than when Cooper introduced the therapy in 1973. Optimum stimulus sites and parameters, if such exist, have yet to be conclusively determined. And finally, the question of the ultimate role of cerebellar stimulation remains: Will it evolve into a major therapeutic approach to epilepsy, or will it be abandoned as an interesting but relatively ineffective medical fad?

SUMMARY

Generalized EEG seizures were elicited in conscious, acute New Zealand albino rabbit preparations by 10 or 15 mg/kg intravenous injections of pentylenetetrazol (PTZ), or by electrical stimulation of the frontal cerebral cortex at 50 Hz, 1 msec monophasic pulse duration and 4.0-7.6 volts for 2 seconds.

Anticonvulsant treatments were applied, either as an intravenous injection of phenobarbital or diphenylhydantoin (DPH), or by electrical stimulation of the simplex and ansiform lobes of the cerebellar hemispheres. Cerebellar stimulation parameters of 10 Hz, 1.5-2.0 msec charge-balanced biphasic pulses, and 3-4 volts were found to be effective in attenuating PTZ induced EEG seizure activity. Deviation from these parameters markedly decreased the effectiveness of the stimuli. After the anticonvulsant treatment, seizures were repeatedly induced with regular incremental increases of PTZ dose or electrical stimulation voltage until a seizure was evoked that approximated the original in severity and duration.

The statistical analysis used four blocks of data: elevations of electrically-induced seizure thresholds by phenobarbital and DPH, and elevations of PTZ seizure thresholds by phenobarbital and cerebellar stimulation. In each case the anticonvulsant treatment was significant at a level of $p<0.025$ or greater.

The elevations of seizure threshold as measured by the percent change in dose or voltage were compared to evaluate the efficacy of cerebellar stimulation in comparison with drug therapies as antagonists of general-

ized seizures. At a significance level of 0.05, the elevation of PTZ seizure thresholds by phenobarbital was greater than that of cerebellar stimulation and greater than the elevation of electrically-induced seizure thresholds by DPH. No difference existed at the 0.01 level of significance.

The statistical significance of the effect of phenobarbital on PTZ seizures was further evaluated by measuring the time after a 10 mg/kg PTZ injection until the occurrence of the first and second paroxysmal bursts in the EEG. The increase in time to the second burst with phenobarbital was significant at the 0.025 level, but the increase in time to the first burst was not significant. The significance of the effect of phenobarbital and DPH on electrically-induced seizures was further evaluated by measuring the EEG seizure durations in response to the same seizure-inducing voltages, both with and without anticonvulsant drug. The decreases in seizure duration with both phenobarbital and DPH were significant at the 0.005 level.

It is concluded that the suppression of generalized seizure activity by cerebellar stimulation does not differ significantly from that seen with DPH or phenobarbital.

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APPENDIX A: ELECTRODE CONSTRUCTION

Figure A1. Electrode construction.

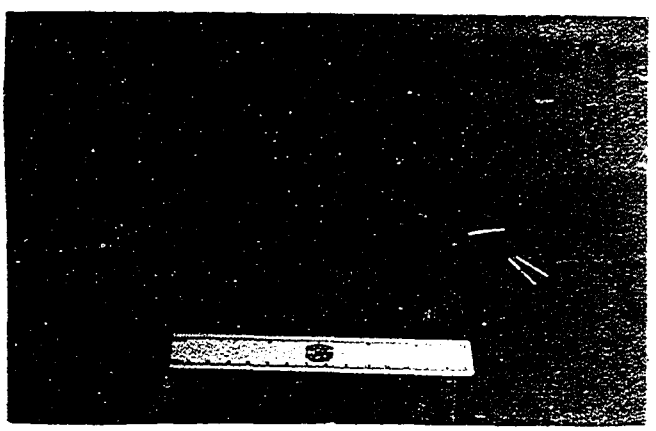
A. Partially-assembled recording electrode, showing uncut twisted-pair wire depth electrodes, and barrel and hub cortical electrode with polyethylene insulation.

B. Assembled recording electrode with depth electrodes cut to desired depth.

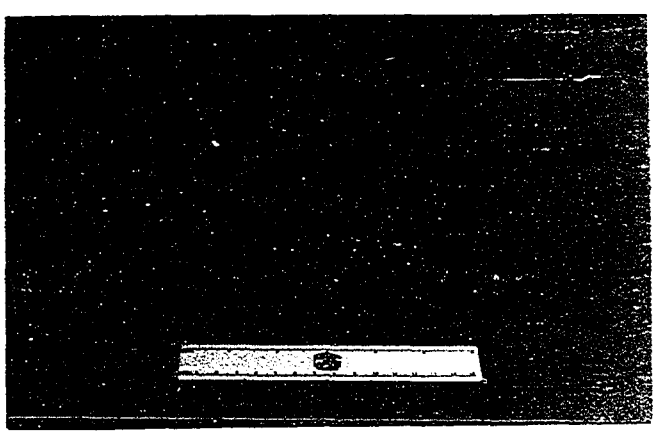
C. Assembled silver ball stimulating electrodes in barrel and hub assembly.

A

B



C



APPENDIX B: SUMMARY OF PARAMETER INVESTIGATION

Table B1. Summary of parameter investigation

Time		Drug	Stimulus				
Real	Elapsed	(dose)	Voltage	Duration	Frequency	On(+)/ Off(-)	Effect
10:06:00	0:00		4.0	1.5	10	+	
	0:15	PTZ (15 mg/kg)				+	twitch
	1:30					-	diffuse spiking
	2:00					+	termination of spiking
	6:30		2.0	1.5	10	+	diffuse spiking
	7:20		2.6	1.5	10	+	termination of spiking
	8:10		2.6	0.15	10	+	diffuse spiking
	8:40		2.6	1.5	10	+	termination of spiking
	9:40		2.2	1.5	10	+	diffuse spiking
	10:45					-	increased spiking
	11:30		3.0	1.5	10	+	termination of spiking
	12:00		2.0	1.5	10	+	diffuse spiking
	12:40		2.6	1.5	10	+	termination of spiking
10:20:20	14:20					-	diffuse spiking
11:17:00	0:00		3.0	1.5	10	+	
	0:15	PTZ (15 mg/kg)				+	twitch
	1:00					+	diffuse spiking
	1:30		4.0	1.5	10	+	termination of spiking
	2:40		3.2	1.5	10	+	diffuse spiking
	3:20		3.4	1.5	10	+	decreased spiking
	4:00		3.6	1.5	10	+	termination of spiking
	5:20		3.6	1.5	6	+	diffuse spiking
	6:10		3.6	1.5	8	+	decreased spiking

Table B1. (Continued)

Time		Drug	Stimulus				
Real	Elapsed	(dose)	Voltage	Duration	Frequency	On(+)/ Off(-)	Effect
	6:30		3.6	1.5	10	+	termination of spiking
	7:10		3.6	1.0	10	+	
	7:40					+	single burst
	8:30		3.6	2.0	10	+	no spiking
	8:45					-	diffuse spiking
	9:30		3.6	2.0	12	+	
	9:40					+	single burst
11:27:10	10:10					-	diffuse spiking