Ouabain Induced Seizures: Site of Production and Response to Anticonvulsants

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SUMMARY: *Ouabain, an inhibitor of Na^+-K^+-ATP'ase, has been administered intraventricularly to rats to study the effect of impairment of membrane transport mechanisms on the genesis of seizures. Running and leaping seizures occur rapidly after injection of ouabain in a low volume (10 µl) when the maximal uptake of ouabain (39.8%) is in the hippocampus. Generalized clonic-tonic seizures are induced by higher volume injections (50 µl) associated with wider distribution of ouabain, including the cerebellum and brainstem.*

Ouabain was injected into cerebral cortex, caudate nucleus, dorsal hippocampus, fastigeal nucleus, ventrolateral mesencephalic reticular formation and cerebellar cortex. The cerebellar injections produced both running and leaping and generalized clonic-tonic seizures. It is suggested that this results from decreased inhibitory effect of vermal and paravermal Purkinje cells on intra-cerebellar nuclei, which alters cerebellar influence on the reticular formation and the limbic system.

Diphenylhydantoin, phenobarbitone, phenacemide, carbamezepine and clonazepam but not ethosuximide are effective against generalized clonic-tonic seizures, suggesting that this is a model for "grand mal" but not "petit mal" seizure mechanisms. It is furthermore suggested that running and leaping are subcortical, probably limbic, seizures that are most relevant as a model for temporal lobe seizures.

RÉSUMÉ: *La ouabaine, un inhibiteur du Na^+-K^+-ATP'ase fut administrée à des rats par voie intraventriculaire afin d'étudier l'effet d'un bloc des méchanismes de transport membranaires sur la genèse des convulsions. Les convulsions saltatoires et cursives se produisent très tôt après l'injection de ouabaine en petit volume (10 µl) lorsque la captation maximale est dans l'hippocampe. Des convulsions généralisées cloniques-toniques sont produites par de plus gros volumes d'injection (50 µl) associés à une distribution plus étendue de la ouabaine, incluant le cervelet et le tronc cérébral.*

La ouabaine fut injectée dans le cortex cérébral, le noyau caudé, l'hippocampe dorsal, le noyau du toit, la formation réticulée mésencéphalique ventrolatérale et le cortex cérébelleux. Les injections cérébelleuses produisent des convulsions saltatoires, cursives ou généralisés. Nous suggérons que cette observation résulte d'un effet inhibiteur diminué des cellules Purkinje vermiennes et para-vermiennes sur les noyaux intracérébelleux, ce qui modifierait l'influence de cervelet sur la formation réticulée et le système limbique.

Le diphenylhydantoin, le phenobarbital, le phenacemide,, le carbamezépine et le clonazepam, mais non l'éthosuximide, sont efficaces contre les convulsions cloniques-toniques généralisées, suggérant que notre modèle s'applique au "grand mal" et non au "petit mal". Nous suggérons enfin que les convulsions cursives et saltatoires sont d'origine sous-corticales, probablement limbiques et qu'elles pourraient servir de modèle des convulsions du lobe temporal.

INTRODUCTION

The multiplicity of experimental seizure models developed in recent years seems to reflect not only the diversity of experimenters, but some uncertainty as to the most relevant and informative approaches to the study of the epilepsies (Purpura et al., 1972). One of many methods has been to use ouabain, which inhibits Na^+ K^+ ATP'ase (Skou, 1965). The use of ouabain allows the experimental study of a possible role of impaired membrane transport in the genesis of seizures. Ouabain has been applied to the cerebral cortex (Lewin, 1970; Petsche et al., 1973; Cornog, 1967), perfused through the inferior horn of the lateral ventricle (Pedley et al., 1969), injected into the septal region (Baldy-Moulinier et al., 1973), and into various subcortical structures (Bergmann et al., 1970).

Previous investigations in this laboratory have studied the effect of intraventricular ouabain injection to freely moving conscious rats (Donaldson et al., 1971), its binding to subcellular fractions rich in Na^+-K^+ ATP'ase (Donaldson et al., 1973), and the response to intraventricular taurine and GABA administration (Izumi et al., 1973a) as well as other amino acids (Tsukada et al., 1974). Two problems have emerged from these studies.

Firstly, the pathogenesis of the seizures is uncertain. The present investigations aim to define further the origin of the seizures by comparing the effects of high and low volume ouabain injections, by measuring the uptake of ^{3}H-ouabain in different brain regions, and by regional injection of ouabain into the cerebral cortex, caudate nucleus, dorsal hippocampus, ventrolateral mesencephalic reticular formation, cerebellar vermis, and fastigeal nucleus. The second problem is the relevance of the model to clinical seizures. Its applicability has been tested by determining the response to a series of anticonvulsants: phenytoin, phenobarbitone, ethosuximide, phenurone, carbamezepine, and clonazepam.

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METHODS

Female Sprague-Dawley rats, weighing between 180 and 210gm, kept under controlled conditions of temperature, humidity and light were used in all experiments. Chronic, indwelling 26G cannulae were inserted in the left ventricle, under sodium pentobarbitone anaesthesia as previously described (Donaldson et al., 1971). Ouabain octahydrate (Sigma Co.) was freshly dissolved in saline or artificial C.S.F. and injected 24-48 hours after cannulation in all experiments except as described in section 5. The duration of injection was 2 minutes.

1. High and low volume injection

Ouabain was administered either in a low volume of 10 μl. or in a high volume of 50 μl. Two dosages were used for each volume: 3 μg., a threshold dose for running and leaping; 10 μg., a higher dose which produces clonic and generalized clonic tonic seizures. Observations were made of the incidence, latency and duration of seizures during the subsequent 15 minutes period.

2. Sequential regional uptake of ^{3}H-ouabain

^{3}H-ouabain, 0.5 μCi (New England Nuclear Corp.) plus 10 μg. of "cold" ouabain was administered in a low volume (10 μl.) or in a high volume (50 μl.) of saline to groups of 12 rats. Four rats from each group were stunned and decapitated at 1, 5, and 10 minutes after the termination of the injection. These times were selected because they approximated the mean time of onset of running and leaping (1.1 min.), focal clonic seizures (4.7 min.), and generalized clonic tonic seizures (8.1 min.). The brains were rapidly removed and dissected into hippocampus, caudate nucleus, hypothalamus, midbrain, medulla oblongata, cerebellum, and cerebral cortex (Glowinski and Inversen, 1966). The regions were homogenized, suspended in Instagel (Packard Instrument Co.), and the radioactivity estimated in a Packard Liquid Scintillation Counter. The results were expressed as:

$$\frac{\text{cpm./gm. for each region}}{\text{Total cpm./gm. for the brain}}$$

3. Regional injections of ouabain

Chronic indwelling 25G cannulae were inserted with the following stereotaxic coordinates (Konig and Klippel, 1963): left cerebral cortex antero-posterior (AP + 6mm., dorso-ventral (DV) + 2.8mm., laterality (lat) 1mm.; caudate nucleus, AP 7.6mm., (DV) + 0.5mm., lat 2.8mm,; posterior dorsal hippocampus, AP + 2.6mm. (DV) + 0.5mm., lat 4.0mm. The cerebellar coordinates (Pellegrino and Cushman, 1967) varied between AP 10 to 10.5mm., DV + 2.5 to + 3.5mm., lat 0-2mm. For fastigeal nucleus (F.N.) and ventrolateral mesencehalic reticular formation (VLMRF) 25G outer cannulae were inserted, containing removable 27G inner cannulae through which ouabain was injected, being introduced 0.5 to 1 mm. beyond the tip of the outer cannulae to the following coordinates (Pellegrino and Cushman, 1967): FN; AP (from bregma) - 9.6mm., DV (from dura) - 4.0mm., lat 1.0mm.; VLMRF, AP - 5.0mm., DV - 7.7mm., lat 2.2mm. The number of rats receiving test and control injections, dosages, and duration of observations are shown in Table 3. At the end of the experiment the brains were removed and placed in 10% formolsaline for subsequent serial sectionning to verity the sites of injection. After VLMRF and FN injections toluidine blue staining of frozen sections (15 micron) was used.

4. Comparison of ouabain in saline with ouabain in CSF

Ouabain was dissolved in artificial CSF, corrected to pH 7.4 by blowing through the solution a 95% 0_2 -5% CO_2 mixture for 10 minutes, and administered in doses of 3 and 10 μg. in 50 μl. The seizure activity was compared with that produced by ouabain in saline, pH 6-6.1.

5. The effect of anticonvulsants on ouabain-induced seizures

The effect of pretreatment with diphenylhydantoin (DPH), phenobarbitone, phenacemide, ethosuximide, carbamezepine, and clonazepam on seizures induced by 5 μg. ouabain in 50 μl. saline was studied. Clonazepam was given subcutaneously in a single dose 2 hours before ouabain. Other drugs were administered intragastrically twice daily for 2 days after cannulation, and once on the third day 4 hours prior to the injection of ouabain. Phenobarbitone, phenacemide, and carbamezepine were administered in a 10% starch solution, DPH in 0.4N sodium hydroxide, and ethosuximide 300 and 450 mg./kg., carbamezepine 150 mg./kg., 250 mg./kg., and clonazepam 2 mg./kg.

RESULTS

1. High and low volume injections

The results are shown in Table 1. There was a significantly higher occurrence of running and leaping with the low volume than with the higher volume at the 3 μg. dose of ouabain. With the higher dose of 10 μg. there was a high occurrence of generalized clonic-tonic seizures when administered in 50 μl. but none with the 10 μl. volume.

2. Sequential regional uptake of ^{3}H ouabain

The percentage of ^{3}H-ouabain in each region of 1, 5, 10 minutes is shown in Table 2. The high uptake of 39.8% in the hippocampus after 1 minute with the 10 μl. volume declined, as the ouabain became more widespread, during the subsequent 10 minutes. With the 50 μl. injections, the distribution was widespread, with slightly less in the hippocampus and higher percentage in the medulla oblongata and cerebellum.

3. Regional injection of ouabain

The results of regional injections of ouabain are shown in Table 3. There was no running and leaping following striatal administration of ouabain, and a low incidence after injection into the cerebral cortex and the dorsal hippocampus. As the volume of these injections was large, it is possible that in the cortical and hippocampal groups some ouabain entered the lateral vertricles. In contrast, running and leaping occurred in 5/6 rats given the same dose in 10 μl. into the left lateral ventricle (Table 1). Control injections of saline had no effects.

Intracerebellar injections in the vermis and perivermal region of lobulus simplex produced running and leaping and generalized clonic-tonic seizures. There was no clear site of

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TABLE I

Intraventricular Injections: Comparison of the Effect of High and Low Volume Injections

Ouabain dose	3 μg.	3 μg.	10 μg.	10 μg.
Volume of injection	10 μg.	50 μg.	10 μg.	50 μg.
Running and leaping				
Number of rats	6	5	9	10
Occurrence	6	1*	6	10
Latency (min.±S.D.)	0.1±0.3	6.4	0.6±0.4	0.1±0.1
Duration (min.±S.D.)	0.4±0.1	0.2	0.6±0.10	0.4±0.5
Clonic-tonic seizures				
Occurence	0	0	0	0

*P<0.05 Occurrence: Number of rats developing seizures

maximal effect but the injection volume of 5 μl. would result in wide diffusion of ouabain. The extent of diffusion was not measured in these experiments, but from estimates of the diffusion of intracerebral dyes, ouabain in 5 μl. may be expected to diffuse over an area exceeding 4 mm. in diameter, possibly with some tracking back beside the cannulae (Myers, 1966). The seizure activity differed from that produced by intraventricular ouabain where running and leaping terminates in post-ictal immobility, with clonic and tonic seizures emerging several minutes later. Following intracerebellar ouabain injections, the phase of wild running and leaping terminated abruptly in forelimb extension, tonic contraction of neck and trunk muscles, and alternating or simultaneous flexion-extension movements of the hindlimbs and elevation of the tail. This was followed by profound post-ictal immobility 10-20 seconds later. The seizures were sometimes triggered by sudden noise or touch. There was considerable variation in latency between 7 and 25 minutes. When seizures developed before 20 minutes, repetitive episodes occurred without seizure-free periods. In these 3 rats the "status epilepticus" continued for up to 90 minutes.

Injection of ouabain into the left fastigeal nucleus produced no abnormality. Administration of ouabain in the VLMRF produced postural abnormalities in all 5 rats and seizures in 4. There was immobility, in a slightly flexed posture, to the extent of remaining motionless when placed over a 2 × 4× 12 cm. bar in the center of the cage. However, in response to increased sensory stimulation, both noise and touch, the rats were able to walk normally. Torsion of the neck and truck occurred in 4 rats, developing between 5 and 30 minutes after injection and lasting for up to 180 minutes. The seizure activity consisted of a modified form of running and leaping, with prominence of leaping lasting between 2 and 6 seconds, starting with latencies of 11.6, 22.4, 52, and 160 minutes. The seizures terminate either in the previously noted immobility or in an asymmetrical tonic seizure, with torsion of the body to the right. Minor clonic movements of the jaw and limbs occurred during some episodes. A mild, long-latency postural abnormality and seizures also occurred, however, after a control injection of CSF in 1 rat.

4. Comparison of ouabain in saline with ouabain in CSF

There was no significant difference between the seizure activity after ouabain in CSF compared to ouabain in saline (Table 4).

5. The effects of anticonvulsants on ouabain-induced seizures

The results are shown in Table 5. Diphenylhydantoin abolished the generalized clonic-tonic seizures. Phenobarbital significantly reduced the clonic-tonic seizures at the high dose only. It increased the latency but did not affect the occurrence of running and leaping. Phenacemide and carbamezepine abolished clonic-tonic seizures and increased the latency of onset of running and leaping. Clonazepam reduced clonic-tonic seizures, but only when accompanied by profound somnolence and loss of normal posture.

DISCUSSION

1. Biochemical effects of ouabain

Ouabain has complex biochemical effects, with increased intracellular Na^+ and Ca^{++}, decreased intracellular K^+, and increased extracellular K^+. There are secondary effects on the transport and metabolism of amines, amino acids, and choline. Although altered neurotransmitter function may be important in the production of seizures, the effects of ouabain are non-specific and do not permit, in these experiments particularly, transmitter defects to be identified.

As ouabain has previously been administered in normal saline (Donaldson et al., 1971), it was possible that the seizures were potentiated by the altered ionic milieu arising from the ventricular injection of a large volume of fluid of abnormal pH, without calcium magnesium or bicarbonate. The present experiments show no significant difference in the effects of ouabain in saline and in CSF (Table 4).

2. The site of action of ouabain

The onset of running and leaping within a minute of injection suggests a periventricular site of action, and the region of maximal uptake at this time after a low volume injection is the hippocampus (39.8%). Other studies support the suggestion that seizure activity may arise in the hippocampus. Perfusion of the inferior horn of the lateral ventricle (Pedley et al., 1969) and intraventricular injection of ouabain (Baldy-Moulinier et al., 1973) elicits hippocampal epileptic activity. Bergmann et al. (1970) administered ouabain in solid form in various regions of the rabbit brain and found

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TABLE 2

Regional Uptake of ^{3}H-Ouabain after Intraventricular Injection in 50 µl. or 10 µl. Volumes

RESULTS ARE EXPRESSED AS: $\frac{\text{percentage c.p.m./g. in each region}}{\text{total c.p.m./g. brain}} \pm$ S.E.M.

	10 µl. VOLUME			50 µl. VOLUME		
	1 min.	5 min.	10 min.	1 min.	5 min.	10 min.
Cerebellum	10.0 ± 1.0	21.6 ± 3.7	15.3 ± 4.2	21.3 ± 3.1	11.8 ± 2.4	22.0 ± 5.9
Medulla oblongata	9.7 ± 3.2	9.6 ± 3.2	15.9 ± 6.8	14.1 ± 5.8	15.6 ± 5.9	15.7 ± 1.4
Hypothalamus	15.3 ± 2.6	12.2 ± 2.3	13.5 ± 3.5	15.0 ± 2.4	12.9 ± 1.6	15.7 ± 1.3
Striatum	8.3 ± 1.3	7.0 ± 0.6	8.0 ± 1.7	5.5 ± 1.7	5.9 ± 0.8	10.5 ± 0.9
Midbrain	13.2 ± 1.3	8.9 ± 2.3	11.5 ± 3.5	7.0 ± 0.4	10.1 ± 0.9	10.5 ± 2.6
Hippocampus	39.8 ± 9.7	33.1 ± 5.3	27.5 ± 8.5	22.9 ± 3.6	35.4 ± 5.1	20.2 ± 3.6
Cerebral cortex	7.5 ± 1.4	7.3 ± 2.3	8.5 ± 3.1	7.3 ± 2.4	8.1 ± 22.0	9.9 ± 3.0

TABLE 3

Regional Injections of Ouabain

Region	Number Rats	Dose (µg.)	Volume (µl.)	Occurrence of Seizure Running Leaping	Clonic-Tonic	Duration of Observation (min.)	Other Phenomena
Cerebral cortex	6	3	5	1	0	15	Torsion of trunk and neck, ataxia
	2	-	5	0	0	15	———
Caudate nucleus	5	3	5	0	0	15	Exploratory behaviour, sniffing, chewing
	2	-	5	0	0	15	———
Hippocampus	8	3	5	2	0	15	Exploratory behaviour
	4	-	5	0	0	15	———
Cerebellar cortex	8	3	5	6	6	30	Ataxia
	6	5	5	5	5	30	Ataxia
		-	5	0	0	30	———
Fastigeal nucleus	5	0.6	1	0	0	30	———
	5	-	1	0	0	30	———
Ventro-lateral mesencephalic reticular formation (V.L.M.R.F.)	5	0.3	1	4	4	180	Immobility: torsion to right
	2	-	1	1	1	180	Immobility: torsion to right

the lowest threshold region for seizure activity to be the hippocampus.

Although Bergmann et al. (1970) produced seizure activity with injection of the caudate nucleus, it required a high concentration. We failed to produce seizures with caudate nucleus injection and only one rat in six showed seizure activity when ouabain was administered into the cerebral cortex. It is more surprising that injection of ouabain to the dorsal hippocampus was less effective than intraventricular ouabain, but does not necessarily exclude a role for the hippocampus in running and leaping seizures. The rat hippocampus is a large structure with an extensive surface area exposed to the lateral ventricle. Intraventricular ouabain may diffuse into the hippocampus over an extensive area, where, in addition to its depolarizing effects on pyramidal cells, impaired activity of the inhibitory basket cells could contribute to the increase firing of pyramidal cells. As pathological studies show that the predominant effects of ouabain are swelling of nerve endings and glial cells (Cornog et al., 1967), it might be expected that the pyramid cell axons passing through the striatum oriens and alveus would be relatively preserved.

Generalized clonic-tonic seizures only occured after the high volume injections. Therefore, they are separable from the running and leaping which, although very intense

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TABLE 4

Comparison of the Effects of Ouabain in C.S.F. and in Saline (50 μl. Volume)

	3 μg.		10 μg.	
	NaCl	C.S.F.	NaCl	C.S.F.
Number of Rats	6	5	8	7
Occurrence, R + L	0	1	8	5
Latency (min. ± S.D.)	5.0 ± 2.8	6.8 ± 3.6	0.4 ± 0.2	0.5 ± 0.5
Duration (min. ± S.D.)	0.1 ± 0.2	0.2 ± 0.3	0.6 ± 0.3	0.4 ± 0.8
Clonic-tonic siezures	1	0	8	5

TABLE 5

The Effect of Anticonvulsants On the Occurrence of Ouabain-Induced Seizures

Drug	N	RUNNING AND LEAPING Occurrence	Latency (min.)	Generalized Clonic-Tonic
DPH				
40 mg./ kg doses	8	6	0.9±0.26	0*
80 mg./ kg. doses	8	4	1.26±0.26	0*
Control	7	6	1.07±0.18	4
Clonazepam				
2 mg / kg doses	9	9	0.47±0.05	0**
Control	6	6	0.60±0.05	5
Ethosuximide				
300mg / kg doses	8	7	0.78±0.19	2
450 mg / kg doses	7	7	0.70±0.71	1
Control	8	8	0.42±0.04	4
Phenacemide				
250 mg / kg	6	6	1.11±1.3	0**
375 mg / kg doses	8	8	1.28±0.21	0**
Phenobarbitone				
30 mg / kg	6	6	0.79±0.12	2
60 mg / kg	7	5a	0.89±0.17	0**
Carbamezepine				
150 mg / kg doses	7	6	0.86±0.06	0**
250 mg / kg doses	6	5	1.45±0.12	0**
Control	8	8	0.43±0.05	6

*$p < 0.05$ **$p < 0.01$ a = significant reduction in leaping but not running

with the high concentration, low volume injections, did not progress to clonic-tonic seizures. ^{3}H-ouabain studies showed that the uptake after 50 μl. injections was higher in the cerebellum. The effect of intracerebellar injections was therefore studied.

Intracerebellar ouabain in the vermis and perivermal region in lobulus simplex produced running and leaping followed by generalized clonic-tonic seizures (Table 3). The sensitivity to external stimuli, the termination of running seizures immediately in clonic-tonic seizures, and the tendency to a prolonged series of seizures shows a difference from the effect of intraventricular ouabain. The seizure pattern is more akin to that observed in this laboratory with allylglycine (D. Davidson, unpublished observations) which is reported to inhibit glutamic acid decarboxylase, reduce GABA concentrations (Alberici et al., 1969; Horton and meldrum, 1973), and produce marked swelling of glia and nerve endings, particularly in the cerebellum (De Robertis et al., 1969).

Cerebellar stimulation and ablation have shown that the cerebellum may have a role in limiting the severity and the duration of seizures induced by electrical, cobalt, or penicillin induced seizure activity in the cerebral cortex (Iwata and Snider, 1959; Dow, 1965; Hutton et al., 1972). Cerebellar stimulation in many studies has failed to elicit seizure activity (Udvarhelyi and Walker, 1965; Ajmone Marsan, 1972). The finding that cerebellar ouabain resulted in seizures without an associated lesion in the cortex or hippocampus is surprising. It cannot, however, be concluded that the seizure activity was generated within the cerebellum, for a sudden alteration in cerebellar inhibitory effects could possibly result in the generation of seizures in other regions. We have found that similar seizures occur with the injection of picrotoxin, a GABA antagonist, into the fastigeal nucleus of the rat (Davidson and Barbeau, 1975) and this suggests that intracerebellar ouabain may have produced a similar loss of inhibitory control by Purkinje cells of the intracerebellar nucleus activity.

Although the intracerebellar nuclei have widespread connections to spinal cord, vestibular, olivary and red nuclei, and the thalamus, two projection systems may be particularly important in the mediation of ouabain effects. One is the fastigeal pathway to the hippocampus, septal region, and orbital cortex (Harper and Heath, 1973). Stimulation of the fastigeal nuclei produces behavioral effects which may be mediated through these pathways (Reis et al., 1973) and variable effects on hippocampal seizures (Babb et al., 1974). As the hippocampus and associated limbic system may be involved in running and leaping seizure activity after intraventricular ouabain, sudden alteration of cerebellar control of these regions would result in similar seizures. The other important projection system is to the reticular formation. Stimulation of the mesencephalic reticular

formation may result in "freezing", running and leaping (Racine, 1972), and seizures (Bergman et al., 1963). Cooling the reticular formation enhances penicillin induced seizures activity (Testa and Gloor, 1974). The result of ouabain injection into the VLMRF supports the hypothesis that a change in reticular formation activity can result in seizures. However, as seizures also occurred after a control injection of C.S.F., these seizures are not specific to ouabain.

The cerebellar role in seizure activity is of interest in view of the recent reports of the effectiveness of chronic cerebellar stimulation in the control of seizures (Cooper et al., 1973a, b), activity of Purkinje cells (Halpern and Julien, 1972; Julien and Halpern, 1972). It provides some evidence that pathological changes in the cerebellum could alter seizure activity.

3. The effect of anticonvulsants

The only anticonvulsant that was completely ineffective in abolishing ouabain-induced seizures was ethosuximide, which is usually ineffective in clinical practice against temporal lobe and "grand mal" seizures. Other anticonvulsants were effective against ouabain which, at a threshold dose for generalized seizures of 5 μg., provides a sensitive test of anticonvulsant efficacy. Although the abolition of running and leaping seizures was not primarily tested because the threshold dose is 3 μg. ouabain, there were significant increases in latency with phenobarbitone, phenurone, and carbamezepine.

4. The relevance of the ouabain model

The ouabain model may be a useful one if a deficiency of ATP'ase is present in the epilepsies. Early studies of total ATP'ase showed no abnormality (Pappius and Elliot, 1954), but brain tissue from epileptics was found to be relatively inefficient in the reaccumulation of K^+ (Tower, 1965). Recently Rapport et al. (1975) have found depression of ATP'ase in cortical samples taken at operation. These important findings indicate the need for further clinical and experimental studies.

The relevance of running and leaping seizures to clinical attacks is uncertain. Electrical discharges in the hippocampus after direct injection of solid ouabain (Bergman et al., 1970) and after intraventricular administrative (Pedley et al., 1969; Baldy-Moulinier et al., 1973), the maximal uptake of ouabain in the hippocampus, the production of seizures in subcortical areas, the cerebellum and the VLMRF suggest that the seizures arise in the limbic system and related subcortical connections. Their most obvious clinical parallel is the rare running or "cursive" seizure, which probably arises in the limbic system (Chen and Forster, 1973). Cursive seizures are a variant of temporal lobe attacks for which adequate experimental models have not been developed. We suggest that running and leaping seizures may be considered as a model for temporal lobe attacks.

The generalized clonic-tonic seizures clearly have their parallel in "grand mal" attacks.

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