RECENT TRENDS IN EPILEPSY AND ANTI-EPILEPTIC DRUGS

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Despite an abundance of information on clinical and experimental epilepsy and on the drugs effective in its treatment, we are still without a full understanding of the inherent etiology of the epileptogenic focus and the mechanism of action of anticonvulsant drugs. In recent years attention has therefore been mainly directed towards the elucidation of these factors on a neuropharmacological and neurochemical basis.

It was only after the introduction of Dilantin in 1938 that a large number of synthetic compounds belonging to a wide variety of chemical moieties have shown to possess anticonvulsant activity. Examples are Mysoline, Diamox, Milontin, Hibicon, Atrolactamide, Valmid and some diols and unsaturated carbinols. Only a few of these, as Dilantin and Tridione have, however, been accepted for clinical use. None as yet has approached the ideal anticonvulsant–one which would be effective for all seizure types and be lacking in toxic properties.

TABLE 1.

Effects of selected anticonvulsant agents on various indices of anticonvulsant efficacy in experimental animals.

Drug	Species	Experimental Indices—(ED_{50} mg./kg.)				
		MES[1]	EST[2] 60 cycle[3]	EST[2] 6/sec.[4]	Pentylenetetrazol[5]	Seizures induced by CO_2 withdrawal[6]
Diphenylhydantoin	mouse	11	——[7]	20.9	——[8]	——
	rat	9	——	——	——[8]	125
	cat	10	——	——	——[8]	——
Trimethadione	mouse	620	650	282	470	——
	rat	361	300	——	300	175
	cat	200	——	——	ca. 150	——
Acetazoleamide (carbon dioxide)	mouse	75	——[9]	——	50–1000[10]	——
	rat	2.5	——[9]	——	?	10

1. Maximal electroshock seizure : end point is abolition of the tonic extensor component.
2. Electroshock seizure threshold : 60 cycle a.c. given for 0.2 sec. and 6/sec. unidirectional pulses given for 3 sec.
3. ED_{50} for 20 per cent elevation in threshold.
4. ED_{50} for two-fold increase in threshold.
5. Protection by drug against seizures induced by CD^{97} of pentylenetetrazol.
6. Clonic seizures which result from sudden withdrawal of rats from 35 to 50% $C0_2$ concentration.
7. Single doses of diphenylhydantoin elevate a.c. EST about 11 per cent in rats.
8. Diphenylhydantoin enhances pentylenetetrazol induced seizures.
9. Single doses of actazoleamide or low concentrations of $C0_2$ elevate EST about 8 per cent in rats and 15 per cent in mice.
10. Doses of acetazoleamide in this range protect a maximum of 50 per cent of mice and delay the onset of seizures.

Neuro-pharmacological studies.

The neuropharmacological approach was based upon investigations of the basic actions of anticonvulsant drugs on neuronal processes. Because of the variety of clinical types of epilepsy and their differences in response to drugs, it is usual to employ a battery of tests to explore the spectrum of anticonvulsant action. Atleast three distinct actions on the neuronal processes can be cited as underlying the effects of anticonvulsants in experimental seizures, viz., stabilisation of the neuronal membrane, decrease in tendency to repetitive discharge and reduction in spread of seizure discharge. All the three actions may underlie alterations of maximal seizure pattern whereas only the first two would appear to be concerned in altering the electrical seizure threshold (EST). These togather with studies of effects of anticonvulsants on synaptic transmission have revealed that certain antiepileptic agents possess one or another of these actions in rather a pure form. Among such agents appear to be Dilantin, Tridione and Diamox.

In the table below are given the spectra of anticonvulsant properties exhibited by these drugs.

TABLE 2.

General characteristics of selected anticonvulsant drugs as revealed by conventional laboratory tests.

DRUGS	Tests			
	CNS depression.	Elevation of EST.	Elevation of pentylenetetrazol threshold.	Abolition of tonic phase of MES.
Diphenylhydantoin	0	+	0[1]	++++
Trimethadione	+	+++	++++	+
Acetazoleamide (carbon dioxide)	+	+	+	++++

TABLE 3.

Effects of selected anticonvulsant drugs on spinal cord synaptic transmission.

DRUGS	Effects				
	Depression of monosynaptic spike.	Depression of polysynaptic response.	Decrease in response to repetitive stimulation.	Antagonism of anticonvulsant effects by pentylenetetrazol.	Depression of post-tetanic potentiation.
Diphenylhydantoin	+	++	+	0[1]	++++
Trimethadione	0	++	++++	++++[2]	0
Acetazoleamide (carbon dioxide)	+++	+	0	0[1]	+

1. Pentylenetetrazol does not reverse the effects of the indicated anticonvulsant, but the indicated anticonvulsant slightly modifies the excitant effects of pentylenetetrazol.
2. Effects of trimethadione are completely reversed by appropriate doses of pentylenetetrazol.

Dilantin and Diamox abolish the tonic phase of the maximal seizures primarily by reducing the spread of seizure discharge. These are, therefore, threshold-stabalizers and seizure-limiters. Diamox, however, has a marked depressant action on the monosynaptic pathway and thus appears to effect some neuronal processes more critically concerned in the spinal cord monosynaptic pathway than in polysynaptic circuits. Tridione is relatively ineffec-

tive in abolishing the tonic phase of MES and has a marked ability to elevate seizure threshold (EST) and a striking elevation of metrazol-threshold. It is, therefore, a threshold raiser and lacks the ability of modifying the seizure pattern.

Neurochemical studies.

The above findings have been explained by Woodbury and Esplin on the basis of recent neurochemical investigations of anticonvulsant drugs.

A. (1) *Brain electrolyte, acid-base and aminoacid metabolism.*

Dilantin and Diamox have been found to decrease markedly the brain intra-cellular Na concentration and increase the ratio of extra-cellular to intra-cellular Na concentration. They, therefore, enhance the action of the Na-pump of the brain neurones. Apart from this, the two drugs possess markedly different neurochemical properties although they produce similar neurophysiological response culminating in anticonvulsant action. Dilantin does not change the ratio of intra-cellular to extra-cellular K in brain while Diamox significantly increases this ratio. Dilantin decreases the cellular total $C0_2$ concentration (calculated as a decreased intra-cellular—$H\bar{C}0_3$ concentration and pH), while Diamox increases the brain cellular total $C0_2$ concentration. Dilantin decreases glutamic acid (GA) and increases Glutamine (Gl) concentrations, thus markedly reducing the GA/Gl ratio. The concentration of Aminobutyric Acid (GABA) was only slightly increased. In contrast, Diamox increased both GA and Gl concentration and, therefore, the ratio GA/Gl was not significantly affected. The concentration of GABA was also significantly increased. The changes in free amino-acids produced by Diamox are similar to those produced by 12.5% $C0_2$, further suggesting that this carbonic anhydrase inhibitor exerts its action by causing accumulation of $C0_2$ in brain eells. In as much as the changes in amino acids, induced by Diamox seem to be significantly related to changes in the glutamic acid-glutamine system, the active transport of the Na may be clearly coupled to this system. In contrast the effect of Diamox to inhibit the Na-influx into brain cells seems to be unrelated to amino acid changes but to involve the enzyme carbonic anhydrase.

2. *Relation between brain excitability, brain electrolyte and brain amino acid metabolism.*

An increase in EST (decrease in brain excitability) is accomplished by an increase in two independent neurochemical factors, viz., the Na ratio, and the GABA concentration. A close relationship between changes in EST and in those GA/Gl ratio has also been noted. Mechanism of anticonvulsant action

of Dilantin and Diamox has thus been put on a neuropharmacological and neurochemical basis. Much further work is needed to understand the mechanism of the Na-pump and the role of GA-Gl system in the regulation of the active-ion transport.

B. *Importance of brain glutamic acid and its metabolites in relation to convulsions.*

Much effort has been expended, without any conclusive results,, in the attempt to corelate the epileptic condition with abnormal constituents of systemic metabolism. It would seem that any chemical change or events peculiar to epilepsy would possibly be found only in epileptogenic foci. The studies of Penfield and associates indicate a probable impairment of local circulatory control in the neighbourhood of these foci. This could cause acute and chronic changes in the chemical environments of neurons such as variations in local concentration of 0_2 glucose, $C0_2$, (acetylcholine Ach.) and/or other metabolic product and pH. Some basic substances like NH_3, amine, Ach. orphosphocreatine or methionine sulphoximine has also been postulated to be the "excitatory" agent for convulsions. The effect of GA in detoxifying the brain NH_3(by glutamine formation), coupled with its inhibition of convulsions in animals, retardations of attacks in petitmal epilepsy and increase of mental alertness was probably the basis of the NH_3-postulate. As GA does not antagonize experimental electroshock convulsions in normal rats and glutamine and asparagene have been shown to be totally devoid of any anticonvulsan action in a battery of six tests (Goodman et al., 1957), no definite conclusions can be drawn with regard to the role of NH_3 or glutamic acid. The presence of some guanidine like substance in the blood of epileptic patients which rises sharply at the time of seizures, as observed by Murrey and Hoft man, also,has not been confirmed.

The recent discovery of *GABA in the brain*, formed by the decorboxylation of GA, has received interest in the metabolism of brain amino-acids. Identification of GABA as the Florey's Inhibitory Factor (Factor I of the brain) in 1953-56 and the further discovery that depletion of GABA may be of importance in explaining the "Vitamin B_6 deficiency" seizures and the "Hydrazide" seizures had directed attention to 'Inhibitory' or 'Regulator Substance' rather than the 'Excitatory' agents in the search for the neurochemical basis epilepsy.

GABA in convulsive seizures. Intraventricular administration of GABA can prevent carbazide induced seizures. Hayashi (1956) found that GABA applied directly to the cortex or injected into the carotid artery or into the CSF arrests or inhibits electrically or chemically induced convulsions in dogs. Hawkins and Sarett (1957) reported that GABA or its lactam. 2-pyrolidinone, was active against metrazol and megimide convulsions. As GABA is formed from GA by its specific decarboxylase (optimum pH 6.5) and is removed by

transaminase (pH 8.2), it may be expected that the amount of GABA increases in acidosis and decreases in alkalosis. This would explain the tendency of acidosis to decrease the incidence of epileptic and experimental seizures and of alkalosis to increase them and to produce tetany. It also explains the anticonvulsant action of $C0_2$ and Diamox resulting from a decrease in the intracellular pH followed by a consequent change in the ratio of the rates of GABA formation and its removal. It also confirms the direct relationship of GABA with EST. Thus depletion of GABA in the brain is associated with hyperexcitability while exogenous GABA results in depression of certain brain activities although the exact site of action is not yet clear.

The main significance of the discovery of GABA in the brain may lie less in the importance of GABA itself than in the further development of, in the actions and metabolisms of various substances related to it and of its possible metabolites, which may be of even greater importance for our understanding of inhibitory and excitatory states within the C.N.S.

Other active substances. GABA-like activity has been found in many other substances. The l-β-0H-compound is 10 times and γ-butyrocholine is 500-1000 times more active. The nor-and the homo-compounds (β-alanin and ω-NH_2-valeric acids) are 1/20th and the α-γ-diamino acids only 1/60 as active. On the other hand α-butyrobetaine and the C_6 to C_8 (W-amino acids are excitatory. Although γ-guanidino-acetic acid is some what active, γ-guanidinobutyric and valeric acids, creatine and creatinine and carnitine are excitatory.

Mono-amine oxidase Inhibitors (MA01) as anticonvulsants. The possible use of MAOIs as anticonvulsants, observed by Brodie et al. (1959) constitutes another great advance in the theoretical as well as in the practical aspects of the neurochemical basis of epilepsy. Chen had found that reserpine, though a sedative, lowers the threshold for electroshock and metrazol convulsions in mice. The time course of the effect coincides roughly with the lowering of brain 5-HT and Nor-epinepherine NE). In contrast, chlorpromazine does not lower the brain amines and has no clear cut influence on the electroshock convulsions. Since brain content of amines is increased by MAOIs, it occurred to them that these drugs might antagonize evoked seizures. Iproniazid (INH) JB5I6 and 807 were tried and found to be quite active in suppressing the tonic phase of the extensor component and raised the brain amines level 2-3 fold. JNH did not raise brain amines and had no anticonvulsant effect. In higher doses it facilitated electroshock seizures, presumably by its antipyridoxal action. Dilantin has been reported by Bonnycastle (1958) to elevate brain 5-HT in rats.

It is clear that whereas MAOIs elevate 5-HT and NE brain level and suppress tonic extensor component of electroshock seizures in rats, reserpine in

contrast, releases brain amines and facilitates electroshock seizures. The results do not permit the conclusion that the effects of the drugs are attributable to changes in 5-HT or NE per se but suggest the possibility that a physiologically active amine, released by reserpine and metabolised by MAOI is involved. Harmaline, a reversibly acting MAOI, was also found to raise the brain levels of amines and block the tonic extensor phase in rats.

Epilepsy and myocardial infarction. Another important discovery made in the field of epilepsy is the observation of Harris and Kokernot (1950) regarding the unity of fundamental mechanism of excitations in the brain and the heart. The concept that the mechanism of production of ectopic ventricular impulses in acute myocardial infarction may be due in part to factors that are similar to those which evoke focal cerebral impulses that produce epileptic seizures led to the trial of antiepileptic drugs for suppressor effect upon ventricular ectopic activity. Dilantin and phenobarbitone in sufficient doses have found to be effective in suppressing the discharge of ectopic impulses in acute myocardial infarctions. Other anticonvulsant drugs should also be tested.

Ccrebral cortex and adrenal cortex. Chronic administration of excessive amounts of adrenocortical steroids alters electroshock seizures threshold (EST). DOCA increases EST (decreases excitability). Corticosterone has little effect. The increase in EST by a single dose of DOCA was associated with a decrease in intracellular brain Na, an increase in the E/C to I/C brain Na concentration, increase in brain GA and aspartic acid concentration and adecrease of glutamine and asparagine concentration. Cortisone had opposite effects. DOCA, lowers the brain excitability by the active transport of brain Na across neurones through the acid glutamine system. Aldosterone is less effective than DOCA. It can also be corelated to GABA activity.