Br. J. Pharmac (1983), **78**, 049–055

Effects of some antiepileptic drugs on the repetitive activity of the node of Ranvier

Maria R. Carratú, V. Di Giovanni & Delia Mitolo-Chieppa

Institute of Pharmacology, Faculty of Medicine, University of Bari, Policlinico, I-70124 Bari, Italy

1 Effects of some antiepileptic drugs on the repetitive activity of the node of Ranvier have been tested on frog myelinated nerve fibres.

2 Nerve fibres were stimulated by supraliminal direct current pulses of long duration. Motor fibres responded with a single action potential; sensory fibres responded with repetitive firing at a frequency of about 300/s. Chlordiazepoxide hydrochloride (0.1 mM), phenobarbitone sodium (0.25 mM) or diphenylhydantoin sodium (0.5 mM) suppressed the repetitive activity.

3 Sensory and motor nerve fibres stimulated by a 10 kHz alternating current of strength twice the threshold responded with repetitive firing at a frequency of 400–500/s. Superfusion of the node with chlordiazepoxide hydrochloride (0.2 mM), phenobarbitone sodium (0.5 mM) or diphenylhydantoin sodium (1.7 mM) reduced the frequency of firing by 50% either in sensory or in motor fibres activated by a.c. stimulation; at the same concentrations, the drugs altered amplitude of the action potential and threshold for electric excitability by less than 10%.

4 Unlike local anaesthetics, chlordiazepoxide, phenobarbitone and diphenylhydantoin are more selective in inhibiting repetitive firing than in reducing the amplitude of the action potential or increasing the threshold for electric excitability.

5 Trimethadione (up to 5 mM) was ineffective on repetitive firing elicited either with direct or with alternating current.

Introduction

Most types of epileptic seizure are initiated by a high-frequency firing from an epileptogenic focus in the brain; under suitable precipitating circumstances this abnormal activity may spread to neighbouring normal neurones so that large parts of the brain, or even the whole brain, undergo a paroxismal activation. It is believed that, once initiated, the seizure is maintained by re-entry of excitatory impulses as in a feedback loop which may also become independent of the triggering focus. Antiepileptic drugs are believed to act mainly on the normal neurones by lowering their responsiveness to epileptogenic stimuli originating in the focus and by controlling the spread of excitation. The specific pharmacological effects reported are: elevation of excitatory synaptic threshold, potentiation of presynaptic or postsynaptic inhibition, prolongation of refractory period and reduction of post-tetanic potentiation (for references see: Jasper, Ward & Pope, 1969; Woodbury, Penry & Schmidt, 1972). Apart from their actions on the membranes of nerve cell soma, dendrites and synaptic endings, some antiepileptic agents can modify permeability and excitability of the axonal membrane (Rosenberg & Bartels, 1967; Blaustein, 1968; Toman & Sabelli, 1969; Lipicky, Gilbert & Stillman, 1972; Mitolo-Chieppa & Marino, 1972; Grossman & Jurna, 1974; Neuman & Frank, 1977; Schwarz, 1979), as well as of other cell membranes, namely of cardiac muscle (Strauss, Bigger, Basset & Hoffman, 1968) and smooth muscle (Melacini, Furlanut, Ferrari & Dalla Volta, 1975).

In the present study we have examined the effects of some antiepileptic drugs on spike frequency in the isolated nerve fibres of the frog. In order to obtain a model of regular repetitive firing allowing a quantitative evaluation of the effects of the drugs, various techniques were envisaged. Spontaneous firing of axons may be induced by lowering the external Ca^{2+} concentration in the bathing medium (Rosenberg & Bartels, 1967; Toman & Sabelli, 1969; Neuman & Frank, 1977). In frog node of Ranvier, repetitive activity may be induced by lowering by 95% or more the external Ca^{2+} concentration and adding tetraethylammonium (5 mM) to the medium (Bergman, Nonner & Staempfli, 1968). Such a procedure was discarded in our experiments since modification of ion concentrations and presence of tetraethylammonium could affect the activity of the drugs under investigation. Another procedure which generates repetitive activity is an appropriate technique of stimulation; when stimulated by a long lasting pulse of direct current, sensory fibres, but not motor fibres,

0007-1188/83/010049-07-$01.00

respond with repetitive firing (Schmidt & Staempfli, 1964). In contrast, as shown by Bromm and Rahn (Bromm, 1968; Bromm & Rahn, 1969, Bromm, 1975), alternating currents with frequencies between 4 and 20 kHz and of appropriate strength cause both sensory and motor fibres to fire repeatedly, even for seconds, at frequencies up to 550/s. In the present experiments we used these techniques of stimulation in order to obtain from frog isolated fibres a long lasting and regular repetitive firing at high frequencies. Under these experimental conditions, we studied the modifications in the frequency of the action potential induced by superfusion of the node of Ranvier with chlordiazepoxide, phenobarbitone, diphenylhydantoin or trimethadione. The first three drugs (listed in decreasing order of potency) reduced the frequency of firing considerably, whereas trimethadione did not induce significant modifications.

Methods

Preparation of the isolated node of Ranvier

Single myelinated nerve fibres, dissected free from the sciatic nerve of the frog, *Rana esculenta*, were transferred to a special chamber (as described by Staempfli, 1959) where one node of Ranvier was continuously superfused with Frog Ringer solution. The superfused node was placed in a small slit across a thin polyethylene tube that was connected to a special stopcock which allowed a rapid change from one bathing medium to another. The neighbouring nodes and the nerve trunks on either side of the dissected region rested in separate compartments filled with 1% cocaine-Ringer solution in order to avoid activity of other nodes apart from that under study; the compartments were separated by air gaps from the tube containing the test node. Electrical contact with the compartments and the tube was made through KCl-agar bridges by means of Ag-AgCl electrodes. The temperature of the bathing medium was 19–21°C.

Electrical stimulation of the node with direct or alternating current and recording of action potentials

The direct current stimulation was performed with supraliminal rectangular pulses (about 20 mV) of long duration (20–25 ms). The alternating current stimulation was performed with alternating positive and negative rectangular pulses of about 20 mV; the duration of each pulse was 50 μs and their frequency was 10 kHz. The pulses were strictly symmetrical to the zero line. For further technical details, consult Bromm (1975). Trains of 100 ms duration were applied between one compartment and the tube which was held at ground potential. The activity of the superfused node was recorded by use of the air-gap method (Staempfli, 1959). Potential differences between the node and the other compartment were recorded by means of a differential amplifier of high input impedance in a negative feedback arrangement (Schmidt & Staempfli, 1966) connected to a double beam oscilloscope.

Experimental protocol

The experiments were carried out on sensory and motor nerve fibres. During superfusion with Ringer solution, the fibres were first stimulated by supraliminal direct current pulses of long duration. The motor fibres, which accommodate quickly, responded with a single action potential; the sensory fibres, which accommodate very slowly, responded with repetitive firing (Schmidt & Staempfli, 1964); such stimulation enabled us to test the drugs only on the repetitive activity of sensory fibres. A regular repetitive firing of high frequency was obtained either for sensory or for motor fibres by trains of 100 ms duration of a 10 kHz alternating current. The strength of the current was increased progressively till a single action potential was obtained (threshold strength). Then the current strength was set at twice threshold strength and the frequency of response of the node was recorded under superfusion, first with normal Ringer solution (controls) and then with the test drug dissolved in Ringer. Reversibility upon drug withdrawal was checked.

Solutions and drugs

The Ringer solution had the following composition (mM): NaCl 110.5, KCl 2.5, $CaCl_2$ 1.8 and $NaHCO_3$ 2.4. The following drugs were used: phenobarbitone sodium (Bracco); chlordiazepoxide hydrochloride (Hoffman-La Roche); trimethadione (Abbott); diphenylhydantoin sodium (Sigma Chemical Co.); lidocaine hydrochloride (Byk Gulden). The concentrations refer to the active component. At the concentrations used in this study, all the drugs were readily soluble in Ringer solution. Solutions were adjusted to pH 7.1–7.2 with Tris buffer.

Results

Figure 1 shows the repetitive activity of about 300/s frequency, recorded from a sensory fibre stimulated by a long lasting pulse of direct current, during superfusion with Ringer only (control, Figure 1 (a)) and during superfusion of one of the anticonvulsants dissolved in Ringer (phenobarbitone, Figure 1 (b)).

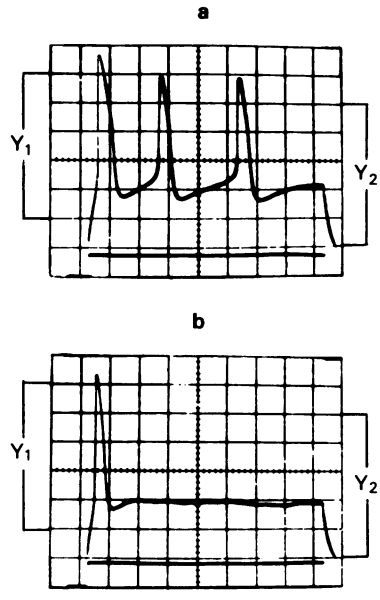

Figure 1 Effect of phenobarbitone (0.25 mM) on repetitive activity of sensory fibre, stimulated by direct current pulses of long duration. Abscissa scale: 2 ms/square; ordinate scale: 20 mV/square.

Chlordiazepoxide (0.1 mM), phenobarbitone (0.25 mM) and diphenylhydantoin (0.5 mM) suppressed the repetitive activity leaving almost unaltered the first action potential; slightly lower concentrations tested for each drug were ineffective and a dose-related reduction of spike frequency was not found. Trimethadione, even at concentration as high as 5 mM, did not produce any significant effect. Figure 2 shows the electrical activity recorded from one node of Ranvier stimulated with trains of 10 kHz alternating current of twice the threshold strength. In this figure, for convenience of demonstration, a time of stimulation of only 35 ms has been chosen; standard experiments were performed with 100 ms stimulation. As long as the nerve fibre was stimulated, the node responded with a regular repetitive firing and the mean 'resting' potential (between spikes) depolarized slightly. Figure 2 (a) shows the activity during superfusion of the node with Ringer solution only (control): under these conditions the frequency of spikes ranged from 350 to 550/s. When the same node was superfused with one of the anticonvulsants dissolved in Ringer, the frequency of firing, under identical conditions of stimulation, might be altered, according to the drug used and its concentration (e.g., Figure 2b; see also Table 1). In order to examine whether there is a difference in responsiveness between sensory and motor nerve fibres, the mean percentage reductions in the frequency of firing (with reference to the controls) at different concentrations of drugs were calculated in a set of sensory and in a set of motor fibres, respectively. Figure 3 shows the corresponding log concentration-inhibition curves. These results show that sensory and motor nerve fibres activated by alternating current stimulation do not differ significantly from each other in their responsiveness to the tested drugs. Table 1 presents the mean frequencies of firing in the controls and during treatment with chlordiazepoxide, phenobarbitone, diphenylhydantoin or trimethadione, at different concentrations; for statistical comparison between the means the *t* test for paired observations (Steel & Torrie, 1960) was used. The first three drugs, at appropriate concentrations, reduced significantly the frequency of firing, whereas trimethadione, even at concentra-

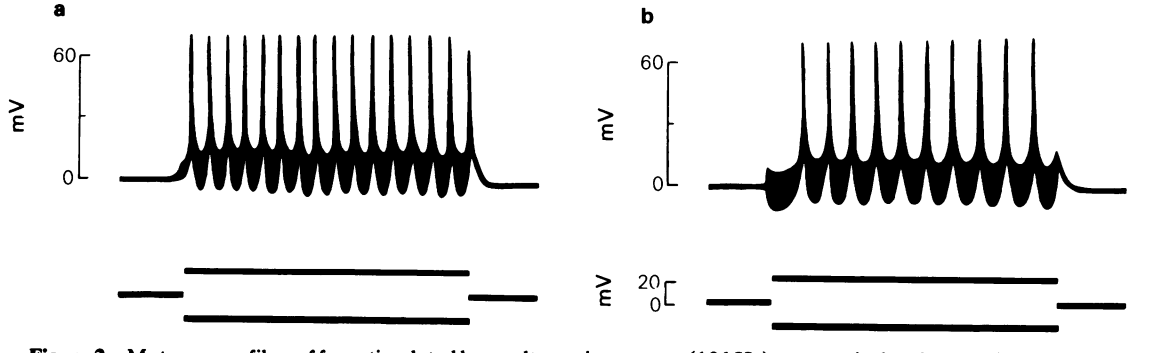

Figure 2 Motor nerve fibre of frog stimulated by an alternating current (10 kHz) symmetrical to the zero line and of strength twice the threshold. The fast change in polarity of the alternating current (every 50 μs) is not visible in the time scale of the records; consequently the stimulus (lower trace) appears as two parallel straight lines equidistant from the zero line and the record of the membrane potential (upper trace) appears as a broad band since it oscillates with the same frequency as the stimulating current around a mean value. Duration of the stimulation = 35 ms. (a) The fibre is perfused with normal Ringer (control). Estimated frequency of firing = 450 spikes/s. (b) The same fibre perfused with Ringer plus phenobarbitone (0.25 mM). Estimated frequency of firing = 290 spikes/s.

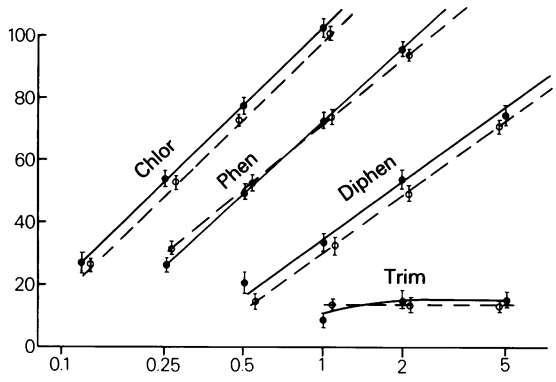

Figure 3 Reduction in the frequency of firing following treatment with some anticonvulsants: Chlor = chlordiazepoxide; Phen = phenobarbitone; Diphen = diphenylhydantoin; Trim = trimethadione. Unbroken line: motor fibres (5 experiments). Broken line: sensory fibres (5 experiments). No statistically significant difference between sensory and motor nerve fibres. Ordinate scale: mean percentage reduction in the frequency of spikes, with reference to the controls. Abscissa scale: (log scale): concentration of the drug (mM). Curves drawn by eye.

tions as high as 5 mM, did not significantly alter the frequency. The concentrations which produced a 50% decrease in the frequency were respectively: chlordiazepoxide 0.2 mM, phenobarbitone 0.5 mM, diphenylhydantoin 1.7 mM; with ratios of relative inhibitory potency approximately 8.5:3.4:1.

After exposures of up to 15 min, the effects of the drugs were promptly reversible upon withdrawal and washing with normal Ringer solution. It is noteworthy that although the concentrations tested in our preparation cannot be related to those achieved clinically since they are 5–10 fold higher, the ratios of the relative potency of the drugs *in vitro* are consistent with the ratios of their antiepileptic activity *in vivo* (Rall & Schleifer, 1980). Table 2 shows the effects of chlordiazepoxide, phenobarbitone, diphenylhydantoin and trimethadione on spike frequency, amplitude of the action potential and threshold for electrical excitability. The concentration that reduced the spike frequency by 50%, reduced the amplitude of the action potential and the threshold for electrical excitability by less than 10%. In contrast, during superfusion with lidocaine, the three effects appeared to run in parallel.

Discussion

Effects of antiepileptic drugs on repetitive firing

The present investigation was concerned with the action of some antiepileptic drugs on the rate of repetitive firing in nerve fibres *in vitro*. Repetitive activity was induced by stimulating nerve fibres with direct current (sensory fibres) or high-frequency alternating current (Bromm, 1968; Bromm & Rahn, 1969; Bromm, 1975). This procedure enabled us to test the effects of some antiepileptic agents in a highly reproducible preparation, without altering the ion concentrations in the medium. Our results show that superfusion of the node with chlordiazepoxide, phenobarbitone or diphenylhydantoin significantly reduces the frequency of firing; this effect is promptly reversible upon withdrawal of the drugs. Under these experimental conditions trimethadione has practically no action on spike frequency. No difference in responsiveness to the drugs was found between sensory and motor nerve fibres as shown in the experiments with alternating current which allowed examination of the repetitive activity in both sensory and motor nerve fibres (see Figure 3). Thus, it can be stated that the nerve fibre, either motor or sensory, can be considered purely as a channel for information transmission. Our results are in agreement with those

Table 1 The frequency of action potentials (expressed as mean number of spikes/s ± s.e.) as influenced by some anticonvulsants, at different concentrations

Concentration (mM)	*Chlordiazepoxide*	*Phenobarbitone*	*Diphenylhydantoin*	*Trimethadione*
0.00 (Control)	450 ± 21	430 ± 19	480 ± 20	470 ± 23
0.12	330 ± 18			
0.25	200 ± 23	310 ± 20		
0.50	100 ± 20	210 ± 17	380 ± 15	
1.00		110 ± 22	320 ± 18	430 ± 25*
2.00			220 ± 19	400 ± 27*
5.00			120 ± 21	400 ± 30*

Each result is calculated from 10 experiments on sensory and motor nerve fibres. The differences between the frequencies recorded under treatment and in the controls are all statistically significant ($P < 0.01$), except for the results marked with an asterisk (trimethadione).

Table 2 Effects of some anticonvulsant drugs and lidocaine on spike frequency, amplitude of the action potential and threshold for electric excitability in sensory and motor fibres (10 experiments)

Drugs	(mM)	*Spike frequency* (% reduction)	*Action potential* (% reduction)	*Threshold* (% increase)
Chlordiazepoxide	0.10	25	0	0
Chlordiazepoxide	0.25	50	<10	<10
Phenobarbitone	0.25	25	0	0
Phenobarbitone	0.50	50	<10	<10
Diphenylhydantoin	0.80	25	0	0
Diphenylhydantoin	2.00	50	<10	<10
Trimethadione	5.00	0	0	0
Lidocaine	0.10	25	25	40
Lidocaine	0.20	50	50	80

of other investigators; in fact, Rosenberg & Bartels (1967) have tested the effects of the antiepileptic drugs on repetitive activity induced by altering the ion concentrations in the bathing medium; under their experimental conditions, diphenylhydantoin, mephenytoin and phenobarbitone were found to block the spontaneous activity in squid giant axons exposed to sea water containing 25% of the usual concentration of Ca^{2+} and Mg^{2+}. Toman & Sabelli (1969) showed that diphenylhydantoin and phenobarbitone inhibit spontaneous firing resulting from immersion in decalcifying media or in isosmotic phosphate solutions, both in frog sciatic nerve and in squid giant axon; trimethadione proved to be ineffective in this respect. Neuman & Frank (1977) found that diphenylhydantoin and phenobarbitone have a selective action in blocking spontaneous activity by any mechanism which reduces sodium conductance in nerves made hyperexcitable by lowering the Ca^{2+} concentration in the medium. In the guinea-pig taenia coli also, diphenylhydantoin reduces the rate of repetitive discharge during sustained depolarization (Melacini, Furlanut, Ferrari & Dalla Volta, 1975).

Selectivity of antiepileptic drugs in reducing repetitive firing

Inhibition of repetitive firing is brought about not only by some anticonvulsants, but also by other drugs, especially some antiparkinsonian compounds and some local anaesthetics (Rosenberg & Bartels, 1967). This raises the question, for each of these drugs, of its relative selectivity in inhibiting repetitive firing, in comparison with other electrophysiological effects on the axonal membrane.

The effects of chlordiazepoxide, phenobarbitone and diphenylhydantoin on action potential and threshold in the single node of Ranvier of nerve fibres have been studied in parallel with the actions of these drugs on repetitive activity (see Table 2). All the drugs mentioned, at appropriate concentrations, reduced the amplitude of the action potential and increased the threshold for electrical excitability of the node. However, at the concentrations that reduced the frequency of firing by 50%, the threshold for electrical excitability and amplitude of the single action potential were altered by less than 10%. Thus, it is apparent that for chlordiazepoxide, phenobarbitone and diphenylhydantoin the inhibitory action on repetitive firing is more specific than other pharmacological actions of the drugs on the nodal membrane; viz., the reduction in the spike frequency is apparently independent of the increase in the threshold for excitability or the decrease of amplitude of the action potential. For comparison, we have tested the relative potencies of the local anaesthetic, lidocaine hydrochloride, in reducing the frequency of firing as well as the amplitude of the action potential and in increasing the threshold. As shown in Table 2, the three effects appeared to run in parallel. Our results are consistent with those reported by several investigators who have dealt with different classes of compounds that inhibit repetitive firing and also modify other functional parameters of the nerve fibre: spike amplitude and duration, threshold and refractoriness (Rosenberg & Bartels, 1967; Blaustein, 1968; Toman & Sabelli, 1969; Mitolo-Chieppa & Marino, 1972; Grossmann & Jurna, 1974). Thus, Rosenberg & Bartels (1967) compared, for several drugs, the minimal concentration which blocks repetitive firing in squid axons maintained in media with reduced Ca^{2+} and Mg^{2+} to the minimal concentration which blocks the evoked action potential in axons maintained in an unaltered medium. They found that local anaesthetics (procaine, tetracaine) can block repetitive firing at concentrations 1/5 to 1/10 of those required to inhibit the action potential, whereas the antiepileptic agents (diphenylhydantoin, mephenytoin, trimethadione and phenobarbitone) are already effective in blocking repetitive firing at much lower relative concentrations, i.e. 1/30 to 1/100 of the concentrations inhibiting the action potential. Toman & Sabelli (1969)

reported that diphenylhydantoin, at concentrations that have negligible effects on the normal parameters of the electrical activity of large myelinated fibres of the frog sciatic nerve, is effective in inhibiting repetitive firing induced by lowering the external Ca^{2+} concentration.

In conclusion, at least some of the antiepileptic agents are much more selective in inhibiting repetitive firing than other drugs, such as local anaesthetics which produce unselective effects.

Axonal mechanisms of action of the anticonvulsant agents

Obviously, the anticonvulsant action of the antiepileptic agents is to be related mainly to mechanisms operating on the nerve cell body (and dendrites) or at sites of synaptic contacts (Jasper *et al.*, 1969; Woodbury *et al.*, 1972). Yet, the experimental investigations on the axon reveal that some antiepileptic drugs have important pharmacological actions on its membrane. Among them, the inhibitory action on repetitive firing seems to be pre-eminent, though by no means specific since it is lacking in some anticonvulsants and it is shared by other drugs, like many antiparkinsonian agents. To what extent this action may contribute directly to the anticonvulsant activity is at present only a matter of speculation. Two possibilities can be envisaged. First, each axon, considered as a channel for information transmission, is endowed with a maximum capacity that sets a limit to the traffic of impulses. Second, axons travelling through epileptogenic cortical focuses can be stimulated directly and the action potentials initiated ectopically can propagate towards the axon terminal or into the cell body: this latter phenomenon, termed backfiring, might be, according to Pedley (1978), of paramount importance in the onset of an epileptic seizure. Both axonal functions envisaged may be modulated by antiepileptic agents such as chlordiazepoxide, phenobarbitone and diphenylhydantoin, whereas other anticonvulsants, like trimethadione, appear to be devoid of such axonal actions.

This work was supported by a grant from the Italian National Research Council (C.N.R. NO. CT81. 00285.04).

References

BERGMAN, C., NONNER, W. & STAEMPFLI, R. (1968). Sustained spontaneous activity of Ranvier nodes induced by the combined actions of TEA and lack of calcium. *Pflügers Arch.*, **302**, 24–37.

BLAUSTEIN, M.P. (1968). Barbiturates block sodium and potassium conductance increases in voltage-clamped lobster axons. *J. gen. Physiol.*, **51**, 293–307.

BROMM, B. (1968). Die Natrium-Gleichrichtung der underschwelling erregten Membran in der quantitativen Formulierung der Ionentheorie. *Pflügers Arch.*, **302**, 233–244.

BROMM, B. (1975). Spike frequency of the nodal membrane generated by high-frequency alternating current. *Pflügers Arch.*, **353**, 1–19.

BROMM, B. & RAHN, U. (1969). Repetitive Aktivität des isolierten Schnürrings bei Reizung mit nullinien-symmetrischen Strömen. *Pflügers Arch.*, **306**, 153–164.

GROSSMANN, W. & JURNA, I. (1974). The effects of diphenylthiohydantoin on the membrane potentials of rat sensory nerve fibre bundles. *Neuropharmacology*, **13**, 819–827.

JASPER, H.H., WARD, A.A., Jr. & POPE, A. (1969). *Basic Mechanisms of the Epilepsies.* Boston: Little, Brown & Co.

LIPICKY, R.J., GILBERT, D.L. & STILLMAN, I.M. (1972). Diphenylhydantoin inhibition of sodium conductance in the squid giant axon. *Proc. natn. Acad. Sci. U.S.A.*, **69**, 1758–1760.

MELACINI, P., FURLANUT, M., FERRARI, M. & DALLA VOLTA, S. (1975). Effects of quinidine and diphenylhydantoin on membrane resistance in smooth muscle. *Archs int. Pharmacodyn. Ther.*, **213**, 17–21.

MITOLO-CHIEPPA, D. & MARINO, A. (1972). Effetti di un tranquillante (il Clordiazepossido) e di un barbiturico (il Luminal) sull'attività elettrica di fibre nervose isolate di rana. *Boll. Soc. Ital. Biol. Sper.*, **48**, 1042–1044.

NEUMAN, R.S. & FRANK, G.B. (1977). Effects of diphenylhydantoin and phenobarbital on voltage clamped myelinated nerve. *Can. J. Physiol. Pharmac.*, **55**, 42–47.

PEDLEY, T.A. (1978). The pathophysiology of focal epilepsy: neurophysiological considerations. *Ann. Neurol.*, **3**, 2–9.

RALL, T.W. & SCHLEIFER, L.S. (1980). Drugs effective in the therapy of the epilepsies. In *The Pharmacological Basis of Therapeutics*, ed. Goodman Gilman, A., Goodman, L.S. & Gilman, A. Sixth edition. pp. 448–474. New York: Macmillan Publishing Co.

ROSENBERG, P. & BARTELS, E. (1967). Drug effects on the spontaneous electrical activity of the squid giant axon. *J. Pharmac. exp. Ther.*, **155**, 532–544.

SCHMIDT, H. & STAEMPFLI, R. (1964). Nachweis unterschiedlicher elektrophysiologischer Eigenschaften motorischer und sensibler Nervenfasern des Frosches. *Helv. Physiol. Pharmac. Acta*, **22**, C143–C145.

SCHMIDT, H. & STAEMPFLI, R. (1966). Die Wirkung von Tetraäthylammonium auf den einzelnen Ranvierschen Schnürring. *Pflügers Arch.*, **287**, 311–325.

SCHWARZ, J.R. (1979). The mode of action of phenobarbital on the excitable membrane of the node of Ranvier. *Eur. J. Pharmac.*, **56**, 51–60.

STAEMPFLI, R. (1959). Is the resting potential of Ranvier nodes a potassium potential?. *Ann. N. Y. Acad. Sci.*, **81**, 265–284.

STEEL, R.G.D. & TORRIE, J.H. (1960). *Principles and Procedures in Statistics.* New York: McGraw-Hill Book Co.

STRAUSS, H.C., BIGGER, J.T., Jr., BASSET, A.L. & HOFFMAN, B.F. (1968). Actions of diphenylhydantoin on the electrical properties of isolated rabbit and canine atria. *Circulation Res.*, **23**, 463–477.

TOMAN, J.E.P. & SABELLI, H.C. (1969). Comparative neuronal mechanisms. *Epilepsia,* **10**, 179–192.

WOODBURY, D.M., PENRY, J.K. & SCHMIDT, R.P. (1972). *Antiepileptic Drugs.* New York: Raven Press.

(*Received April 8, 1982.*
Revised September 6, 1982.)