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EFFECT OF DIPHENYLHYDANTOIN AND LIDOCAINE ON CARDIAC ARRHYTHMIAS INDUCED BY HYPOTHALAMIC STIMULATION

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Research was conducted according to the principles enunciated in the "Guide for Laboratory Animal Facilities and Care," prepared by the National Academy of Sciences - National Research Council.

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ABSTRACT

The importance of the central nervous system in the antiarrhythmic actions of diphenylhydantoin and lidocaine was studied using arrhythmias induced by electrical stimulation of the posterior hypothalamus in cats. Hypothalamic stimulation resulted in cardiac arrhythmias mediated by the sympathetic nervous system. The arrhythmias occurred during stimulation, and recordings from cardiac sympathetic nerves revealed a continuous pattern of hyperactivity during the time of the arrhythmia. Administration of diphenylhydantoin (10-15 mg/kg I.V.) prevented both the arrhythmias and the hyperactivity in sympathetic nerves. Diphenylhydantoin had no effect on similar arrhythmias evoked by electrical stimulation of peripheral sympathetic nerves. Administration of lidocaine (2-6 mg/kg I.V.) prevented the arrhythmias produced by hypothalamic stimulation without attenuating sympathetic hyperactivity, and also prevented similar arrhythmias produced by stimulation of peripheral sympathetic nerves. Results identical to those obtained with lidocaine were observed with methyllidocaine, a quaternary derivative of lidocaine that does not easily penetrate the blood-brain barrier.

These results suggest that the antiarrhythmic action of diphenylhydantoin against neurogenic arrhythmias is due to its central neurodepressant action. The results further suggest that, in contrast to diphenylhydantoin, lidocaine acts at peripheral neural or cardiac sites to antagonize neurogenic arrhythmias.

I. INTRODUCTION

Drugs that affect the rhythm of the heart are generally thought to act by directly altering the electrophysiological properties of myocardial cells. This view is based on numerous experimental studies which have demonstrated that antiarrhythmic drugs exert profound effects on automaticity, membrane responsiveness, refractory period and excitability of myocardial cells in vitro.[9,15,24,27] These studies have greatly increased our understanding of the mechanism of action of antiarrhythmic drugs, but the approach has tended to restrict the focus of attention to the heart, to the exclusion of extracardiac mechanisms.

Results from a small but growing number of studies have suggested that neural hyperactivity may be important in the genesis of several types of arrhythmias,[5,11,28] and that some antiarrhythmic drugs may antagonize these arrhythmias by their effects on the nervous system rather than their direct effects on the heart.[4,11,26] For example, we recently found that administration of toxic doses of digitalis induced cardiac sympathetic hyperactivity concurrent with the development of ventricular arrhythmias and that administration of diphenylhydantoin abolished the neural hyperactivity coincident with reversion to normal sinus rhythm.[7] These results suggested that the neural excitatory actions of digitalis may be responsible for provoking arrhythmias and that the neurodepressant action of diphenylhydantoin may be responsible for its antiarrhythmic effect.

The primary purpose of the present study was to test more directly the hypothesis that the nervous system is a major site of action of diphenylhydantoin in antagonizing cardiac arrhythmias. An additional purpose was to compare the widely used

antiarrhythmic agent lidocaine with diphenylhydantoin to determine the validity of the predominant view that these two drugs have the same mechanism of action.[9]

In approaching this problem we set out to develop a model in which arrhythmias could be induced by stimulation of the brain while the neural activity to the heart could be simultaneously monitored. Our aim was then to study the action of diphenylhydantoin and lidocaine on this model to evaluate the neural component in the antiarrhythmic action of each drug.

II. METHODS

General procedures. Thirty-eight adult cats, unselected as to sex and ranging from 2.0 to 3.4 kg in weight, were anesthetized with an intravenous infusion of alpha chloralose (70-80 mg/kg), administered at a rate of 10 mg/min. After induction of anesthesia, the animals were immobilized with succinylcholine chloride (5 mg I.V.) and intubated. The animals were artificially ventilated with a gas mixture of 98.5 percent oxygen and 1.5 percent carbon dioxide using a Harvard respirator pump (Model 606) set to deliver tidal volumes of 25-40 cm^3 at rates of 25-30 breaths per minute. Continuous ventilation in this manner has been shown to maintain arterial blood pH between 7.31 and 7.43.[20]

Adequacy of anesthesia was determined by the lack of any autonomic response (increase of heart rate or blood pressure) to a painful stimulus in the absence of succinylcholine. When indicated, additional doses of chloralose (5 mg/kg I.V.) were administered to insure adequate depth of anesthesia. The femoral artery and saphenous vein were catheterized for recording blood pressure and administering drugs, respectively. Continuous recordings were made of the electrocardiogram (Lead II) and the

arterial blood pressure, using a Beckman type R B Dynograph. Body temperature was maintained at 37°-38°C with an infrared lamp.

Procedures employed for hypothalamic stimulation. The head of the cat was positioned in a stereotaxic apparatus, and a dorsal medial incision was made in the scalp. A 3-mm hole was drilled through the cranium at the desired anterior-posterior and lateral stereotaxic coordinate, and a bipolar stainless steel electrode (David Kopf NE-200) was lowered to the desired vertical stereotaxic coordinate. Points within the posterior hypothalamus were stimulated to evoke cardiac arrhythmias. The stereotaxic coordinates were: anterior 7.5-9.0 mm, lateral 1.0-2.0 mm, and vertical minus 2 to minus 5 mm.[25]

The stimulating electrode was connected to a Grass stimulator (Model S-4) through a stimulus isolation unit (Model SIU 478 A). Stimuli used were monophasic pulses of 8-14 volts, 1-5 msec in duration, applied at a rate of 80-120 Hz. Tissue resistance was measured between the two electrode poles at the beginning of each experiment and at intervals during the experiment. Tissue resistance ranged from 17 to 24 kohms in various experiments but remained constant during a given experiment. In each experiment, an attempt was made to locate points within the posterior hypothalamus which, when stimulated, produced maximal cardioacceleration and arrhythmias. No attempt was made to duplicate specific stimulation points from animal to animal, rather, points were sought from which the desired cardiovascular response could be obtained.

In preliminary experiments, the arrhythmias produced by electrical stimulation of the posterior hypothalamus were only observed in about 50 percent of the animals.

Changing the site of stimulation within the posterior hypothalamus or changing the stimulus parameters did not increase the occurrence of arrhythmias. A similar lack of consistency in obtaining this type of arrhythmia has been reported by others.[10,13] When arrhythmias failed to occur in our study, an increase in sinus rate was observed and appeared to mask the increase in rate of subatrial pacemakers. Because of this observation and the fact that sympathetic innervation of the sinus node is primarily from the right sympathetic trunk,[21] other preliminary experiments were performed in animals in which the sympathetic nerves on each side of the right stellate ganglion were sectioned. With the sympathetic influence to the sinus node removed, stimulation of the posterior hypothalamus consistently resulted in arrhythmias during stimulation. In addition, arrhythmias could be evoked numerous times in a given animal. Therefore, the right preganglionic and postganglionic nerves to the heart were routinely sectioned in all subsequent experiments described in the present study.

Procedures employed for sympathetic nerve recordings. The stereotaxic apparatus was rotated 90° to allow access to the right thorax, and a thoracotomy was performed with resection of the first three or four ribs and the clavicle. The preganglionic sympathetic nerves to the right stellate ganglion were carefully dissected free from surrounding tissue and sectioned at a point proximal to their entrance into the ganglion. The central cut end of the sympathetic trunk was placed on bipolar platinum recording electrodes. Sectioning the nerve trunk distal to the point of recording was done to assure that only efferent sympathetic nerve activity would be recorded. In addition, as mentioned above, sectioning the right sympathetic nerves allowed us to readily obtain arrhythmias with electrical stimulation of the hypothalamus.

Although all of the results described in the present study were obtained using neurograms from the right cardiac sympathetic nerves, our preliminary studies, as well as studies of other investigators,[1,3] have demonstrated that the neurograms from both the right and left cardiac sympathetic nerves are bilaterally synchronous before and during periods of hypothalamic stimulation.

Nerve activity was amplified using a Tektronix Type 2 A 61 amplifier and was stored on electromagnetic tape. This activity was later displayed on an oscilloscope and photographed. In addition, nerve activity was quantitated by feeding it from the tape into a Grass integrator (Model 7 P10B). Both the nerve activity and the integration of the activity with respect to time were displayed on a Grass polygraph (Model 7). The integrator was reset to zero at 10-second intervals, and the discriminator set so that only the positive activity was measured. Calibration of the integration system with reference to a known input was not done, as we were only interested in relative changes in activity. The method we used to measure the analog output of the integrator is described further in the Results section.

Procedures employed for peripheral sympathetic nerve stimulation. Experiments were also performed in which arrhythmias were produced by electrical stimulation of the cardiac preganglionic sympathetic nerves. The basic preparation was similar to that described above except that cats were subjected to spinal section at C-1 and to bilateral cervical vagotomy. For sympathetic nerve stimulation, the left thoracic cavity was opened by excising the ribs on that side from the mammillary to the midaxillary line. The left sympathetic trunk was dissected with a glass probe from the stellate ganglion to the level of T4 or T5 and sectioned at that point. A bipolar stimulating

electrode was placed on the preganglionic trunk as close to the stellate ganglion as possible. The stimulus used consisted of monophasic pulses of 8-12 volts with a duration of 0.5 to 1.0 msec and a frequency of 20-50 Hz. This spinal preparation was also used to assess the effects of drugs on the chronotropic response to norepinephrine.

Verification of electrode placement. At the termination of randomly selected experiments in which hypothalamic stimulation had been performed, a brain lesion was made at the tip of the electrode with the use of a Grass lesion maker. The brain was then removed and fixed in 10 percent Formalin. Slices of brain containing the lesions were sectioned at a 20-μm thickness with a freezing microtome and stained using the Weil myelin sheath method.[16] Histological sections were examined to identify the site of stimulation and were photographed. Inspection of these photographs revealed that all stimulation sites were located within the posterior hypothalamus.

Data analysis. The data were statistically analyzed by paired comparisons using the Student's "t" test. The criterion for statistical significance was $p < 0.05$.

Drugs used. Diphenylhydantoin (Parke, Davis and Company, Detroit, Michigan) was dissolved in distilled water brought to pH 12 with NaOH. Concentration of the drug was 4 mg/ml, and it was administered by a constant infusion at a rate of 4 mg/min. Lidocaine hydrochloride (Astra Pharmaceutical Products, Inc., Worcester, Massachusetts) was diluted from the stock concentration of 20 mg/ml to 5 mg/ml with 0.85 percent sodium chloride solution and administered as a single injection over a 1-minute period. Methyllidocaine iodide powder was synthesized by Dr. Thomas Mittag (Department of Pharmacology, Mount Sinai School of Medicine, New York, New York) from a lidocaine base supplied by Dr. G. Vinton Hallock of Astra Pharmaceutical Products, Inc.

Methyllidocaine was dissolved in 0.85 percent sodium chloride solution at a concentration of 5 mg/ml and administered as a single injection over a 1-minute period. Other drugs used were: alpha-chloralose (Etablissements Kuhlmann, Paris, France); succinylcholine chloride (Sigma Chemical Company, St. Louis, Missouri); l-arterenol bitartrate (Sigma Chemical Company, St. Louis, Missouri); d,l-propranolol hydrochloride (Courtesy of Ayerst Laboratories, Inc., New York, New York); and propantheline bromide (G. D. Searle and Company, Chicago, Illinois). Except for chloralose, which was dissolved by heating it in distilled water, all other drugs were either diluted or dissolved in 0.85 percent sodium chloride solution. The doses of the drugs were calculated as their salt.

III. RESULTS

Characterization of the arrhythmia. Electrical stimulation of points in the posterior hypothalamus produced an increase in heart rate and blood pressure and an alteration in cardiac rhythm. During hypothalamic stimulation the electrocardiogram revealed a progressive narrowing of the P-R interval until the P wave disappeared and a nodal rhythm predominated. These changes can be seen in panel A of Figure 1. Restoration of sinus rhythm occurred within 5 to 15 seconds after termination of stimulation, and the transition to sinus rhythm appeared to be the reverse of the sequence that marked its occurrence.

The changes observed with stimulation suggested that the arrhythmia was mediated by the sympathetic nervous system. In support of this was the fact that the arrhythmia was always preceded by an increase in sinus rate and was associated with an increase in blood pressure (Figure 1). Furthermore, the rate of the abnormal rhythm

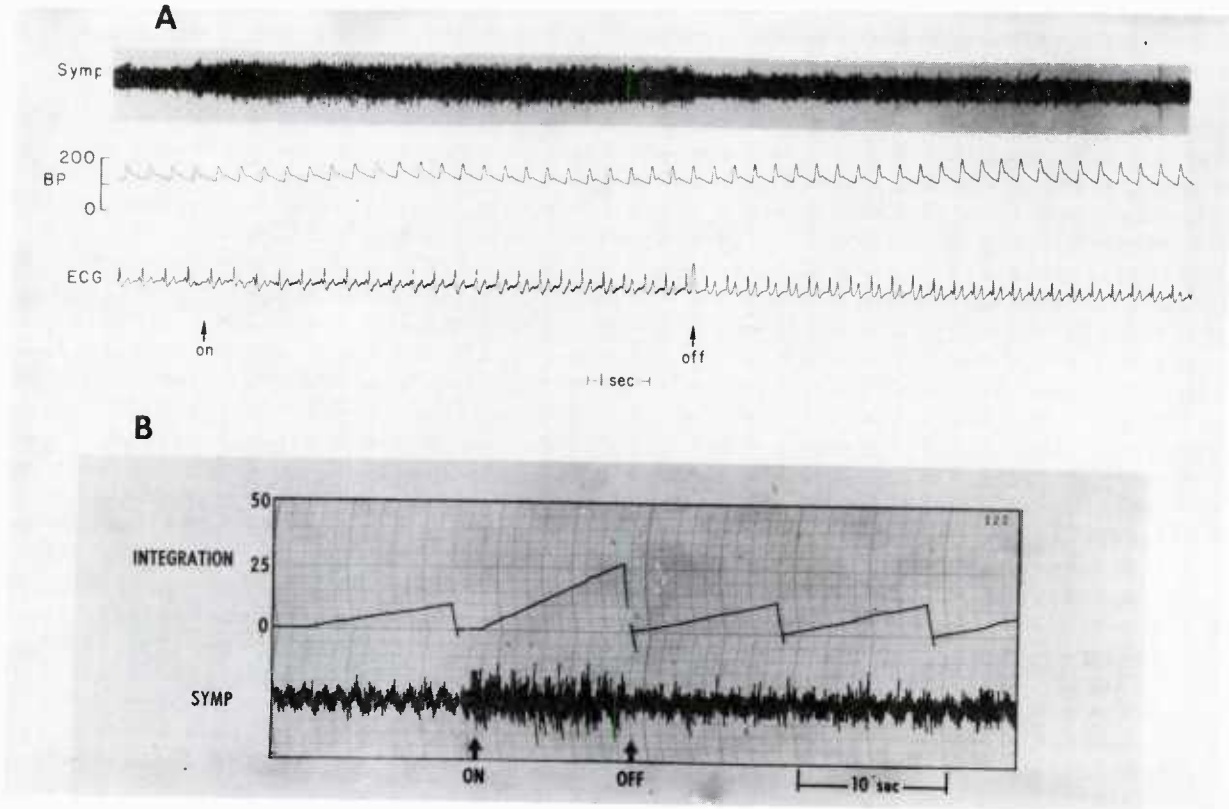

Figure 1. Effects of electrical stimulation of the posterior hypothalamus (as indicated by arrows) on sympathetic nerve activity (Symp), cardiac rate and rhythm (ECG), and arterial blood pressure (BP). Panel A (top insert) shows the changes in sympathetic nerve activity, ECG, and blood pressure. Panel B shows the cumulative integration of the sympathetic nerve activity over 10 seconds.

was always faster than the control sinus rate. Finally, there were other signs of sympathetic hyperactivity, i.e., mydriasis and contraction of the nictitating membrane.

To determine whether the arrhythmia was mediated by the sympathetic nervous system, three experiments were performed in which propranolol (1.0 mg/kg I.V.) was administered after obtaining several control arrhythmias. In all three animals propranolol pretreatment prevented the arrhythmia. To rule out any participation from the

parasympathetic nervous system in the generation of the arrhythmia, four experiments were performed in which either bilateral cervical vagotomy or administration of propantheline (1 mg/kg I.V.) was done after obtaining several control arrhythmias. In none of the four experiments was the arrhythmia prevented. However, subsequent administration of propranolol (0.5 mg/kg I.V.) prevented the arrhythmia from occurring in all four animals. A representative experiment appears in Figure 2.

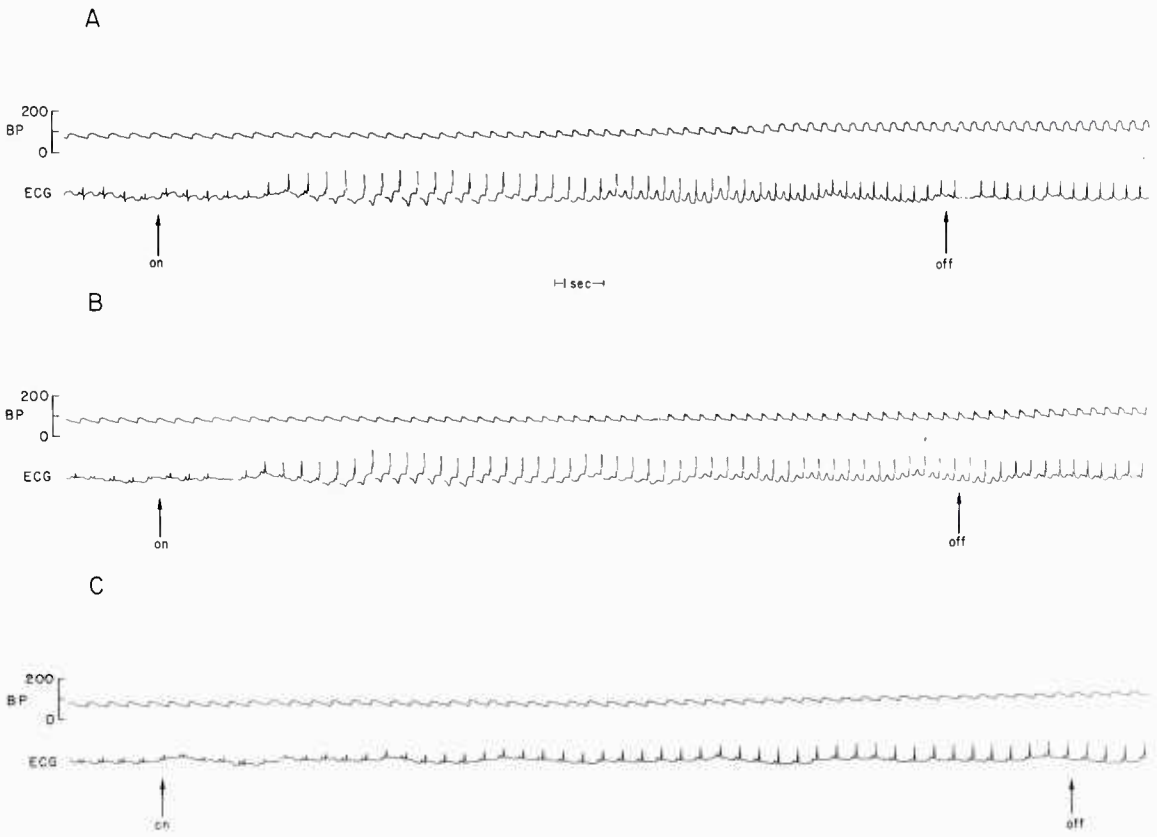

Figure 2. Effects of propantheline and propranolol on cardiac rate and rhythm (ECG) and arterial blood pressure (BP) responses evoked by electrical stimulation of the posterior hypothalamus (as indicated by arrows). Panel A shows control recordings. Panel B shows recordings made 2 minutes after propantheline (1 mg/kg I.V.). Panel C shows subsequent recordings made 2 minutes after propranolol (0.5 mg/kg I.V.).

After obtaining the above results, experiments were performed wherein electrical recordings were made of the cardiac sympathetic nerve activity before and during hypothalamic stimulation. These recordings revealed an increase in neural activity ing hypothalamic stimulation. Both amplitude and frequency of neural activity were increased. A representative experiment appears in panel A of Figure 1.

Quantitation of the nerve activity from these experiments was carried out using the Grass integrator (see Methods), and panel B of Figure 1 shows the records obtained from one experiment. The output of the integrator is such that the slope of the line or the height reached within a given time period is proportional to the cumulative nerve activity during that time. For all experiments the height of the peak recorded after a 10-second sampling period was measured and expressed in millimeters. This value does not represent the actual area under the nerve signal but is proportional to it. Using this procedure it was possible to measure the change in nerve activity caused by various procedures or drugs. For example, in panel B, Figure 1, it can be seen that prior to hypothalamic stimulation, the integrator peak reached 10 mm, whereas during stimulation the peak reached 27 mm. Thus, there was an increase of 17 mm (170 percent) during hypothalamic stimulation in this experiment.

Results summarizing the effects of electrical stimulation of the posterior hypothalamus on blood pressure, heart rate and nerve activity are presented in Table I. They indicate that significant increases in pressure, rate, and nerve discharge occurred during stimulation. The rhythm change developed within a few seconds after the stimulation was initiated and persisted for 10.2 ± 3.24 seconds after the stimulation was terminated. The arrhythmia could be repeatedly evoked as many as 10 times in a

Table I. Effect of Electrical Stimulation of the Posterior Hypothalamus on Mean Arterial Blood Pressure, Heart Rate and Sympathetic Nerve Activity*

Initial			Maximal changes induced by hypothalamic stimulation		
Mean blood pressure (torr)	Heart rate (beats/min)	Nerve activity (mm)	Mean blood pressure (torr)	Heart rate (beats/min)	Nerve activity (percent change)
122 ± 6.1	139 ± 4.9	17.5 ± 1.73	+ 30 ± 4.8†	+ 12 ± 1.2†	+ 76 ± 11.4†

* Data obtained from 22 animals. Values are the mean ± S. E.

† $p < 0.05$ with paired comparisons between values obtained before and values obtained during hypothalamic stimulation

given animal and was always evoked at least three consecutive times before testing the effects of drugs.

Effects of diphenylhydantoin. Six experiments were performed in which diphenylhydantoin was tested against arrhythmias and sympathetic hyperactivity induced by stimulation of the posterior hypothalamus. Hypothalamic stimulation was performed after each 5 mg/kg of diphenylhydantoin were infused until the arrhythmia was prevented. In each of the six animals, administration of 10 to 15 mg/kg (average of 11.7 ± 1.7 mg/kg) prevented both the arrhythmia and the high amplitude sympathetic neural discharge during hypothalamic stimulation. A representative experiment illustrating this effect is presented as Figure 3.

The changes in cardiovascular parameters and nerve activity which occurred in the six experiments with stimulation of the posterior hypothalamus before and after diphenylhydantoin are summarized in Table II. It should be noted that in this and the subsequent table statistical comparison of data was made in two ways. First, comparisons were made between data obtained during hypothalamic stimulation and data

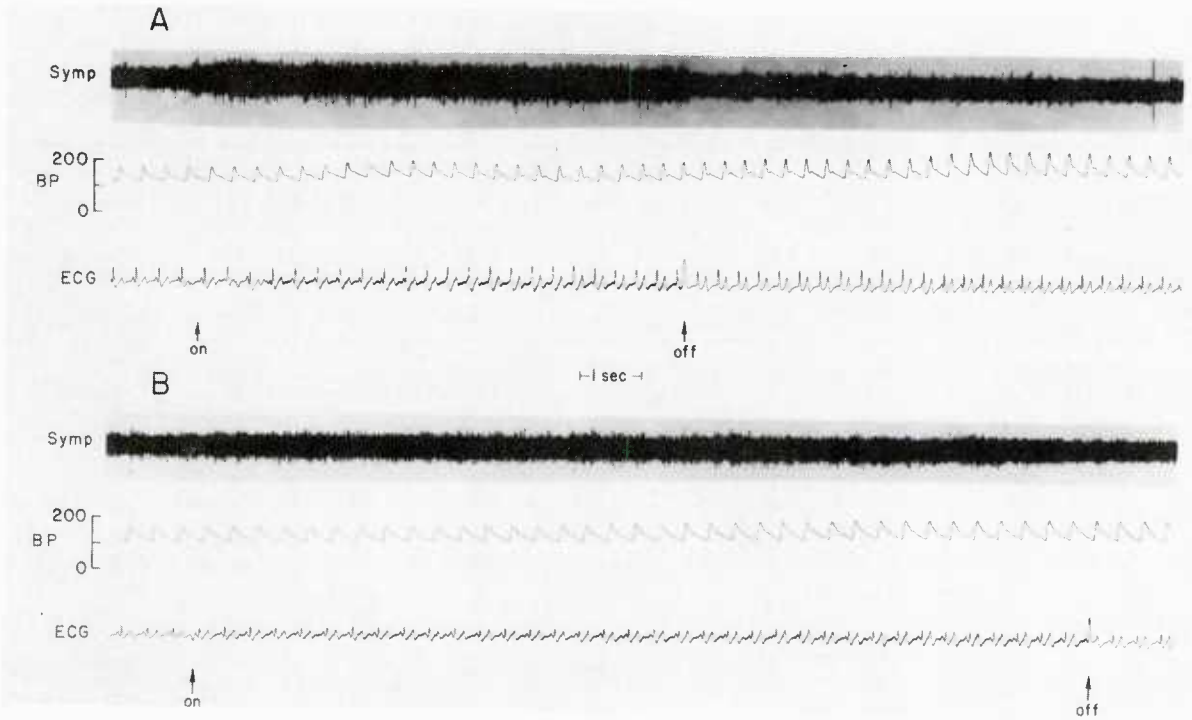

Figure 3. Effect of diphenylhydantoin (DPH) on sympathetic nerve activity (Symp), cardiac rate and rhythm (ECG), and arterial blood pressure (BP) responses produced by electrical stimulation of the posterior hypothalamus (as indicated by arrows). Panel A shows control recordings. Panel B shows recordings made 2 minutes after I.V. administration of 10 mg/kg of DPH.

obtained during the prestimulation period (i.e., horizontal comparisons). Second, comparisons were made between data obtained before and after drug administration (i.e., vertical comparisons) and designated as the mean difference between the two experimental conditions. Prior to drug administration, hypothalamic stimulation resulted in significant increases in mean blood pressure, heart rate and nerve activity. After diphenylhydantoin administration, hypothalamic stimulation produced a significant increase in nerve activity but no significant change in mean blood pressure or heart rate. With the second type of comparison, it can be seen that diphenylhydantoin

Table II. Effect of Diphenylhydantoin on Cardiovascular Responses and Sympathetic Nerve Activity Changes Induced by Stimulation of the Posterior Hypothalamus*

Experimental condition	Initial			Maximal changes induced by hypothalamic stimulation		
	Mean blood pressure (torr)	Heart rate (beats/min)	Nerve activity (mm)	Mean blood pressure (torr)	Heart rate (beats/min)	Nerve activity (percent change)
Responses obtained before administration of diphenylhydantoin	132 ± 10.3	148 ± 4.9	23 ± 3.8	+41 ± 6.9†	+15 ± 2.0†	+64 ± 9.1†
Responses obtained after administration of diphenylhydantoin	130 ± 12.4	134 ± 5.7	20 ± 2.9	+10 ± 6.8	+3 ± 1.8	+29 ± 7.5†
Difference of values obtained before and values obtained after diphenylhydantoin administration	-0.3 ± 3.7	-14 ± 5.6	-4.7 ± 1.3‡	-32 ± 7.2‡	-12 ± 2.5‡	-37 ± 8.6‡

* Data obtained from six animals. Values are the mean ± S.E.
† $p < 0.05$ with paired comparisons between values obtained before and values obtained during hypothalamic stimulation
‡ $p < 0.05$ with paired comparisons between values obtained before and values obtained after diphenylhydantoin administration

administration resulted in a significant decrease in nerve activity during the initial (prestimulation) period and significant antagonism of the blood pressure rise and neural hyperactivity resulting from hypothalamic stimulation. In none of the six experiments was the arrhythmia prevented by diphenylhydantoin without attenuation of sympathetic nerve discharge.

Arrhythmias similar to those evoked by hypothalamic stimulation were evoked in cats with spinal cords transected by stimulation of the left preganglionic sympathetic trunk. In these experiments, sites of drug action within the central nervous system were excluded, making it possible to assess the contribution of peripheral action of the drug in antagonizing neurally induced arrhythmias.

Peripheral sympathetic stimulation, like hypothalamic stimulation, caused a progressive shortening of the P-R interval until a nodal rhythm predominated.

Cessation of stimulation resulted in emergence of the P wave with progressive widening of the P-R interval and a return to sinus rhythm. Four experiments were performed in which diphenylhydantoin was tested against arrhythmias induced by peripheral sympathetic nerve stimulation, and a representative one appears in Figure 4. Stimulation was carried out after each 5 mg/kg of diphenylhydantoin were infused.

In none of the four experiments was the arrhythmia prevented by diphenylhydantoin even though doses of from 20 to 40 mg/kg (average 26.6 $\pm$ 6.7 mg/kg) were administered. Indeed, diphenylhydantoin seemed to aggravate the arrhythmia. During the control period, the duration of the arrhythmia averaged 4 seconds; after diphenylhydantoin, the duration of the arrhythmia averaged 42 seconds ($p < 0.05$). Prolongation of the duration of arrhythmia can be noted in Figure 4.

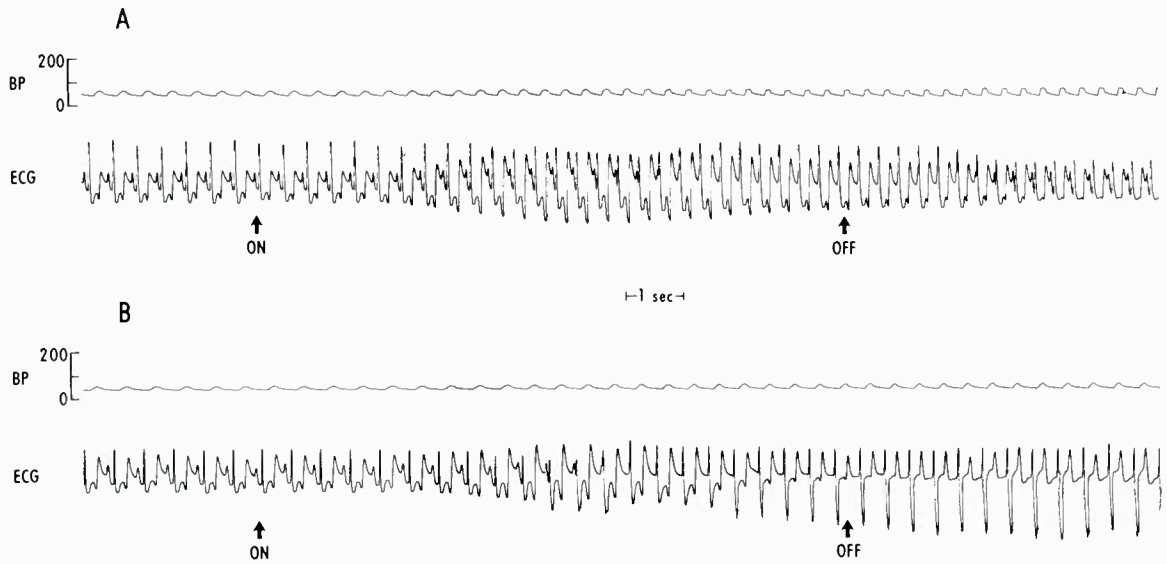

Figure 4. Effect of diphenylhydantoin (DPH) on the cardiac rate and rhythm (ECG) and arterial blood pressure (BP) responses produced by electrical stimulation of the left cardiac sympathetic nerves (as indicated by the arrows). Panel A shows control recordings. Panel B shows recordings made 2 minutes after I.V. administration of 20 mg/kg of DPH.

Effects of lidocaine and methyllidocaine. Four experiments were performed in which lidocaine was tested against arrhythmias induced by posterior hypothalamic stimulation. Hypothalamic stimulation was carried out after each 2 mg/kg of lidocaine were administered until the arrhythmia was prevented. Lidocaine was effective in preventing the sympathetic arrhythmia induced by hypothalamic stimulation in each animal tested, the effective dose being 4.0 ± 0.8 mg/kg. In contrast to diphenylhydantoin, prevention of the arrhythmia was not associated with an alteration of hyperactivity in sympathetic nerves. A representative experiment is shown in Figure 5.

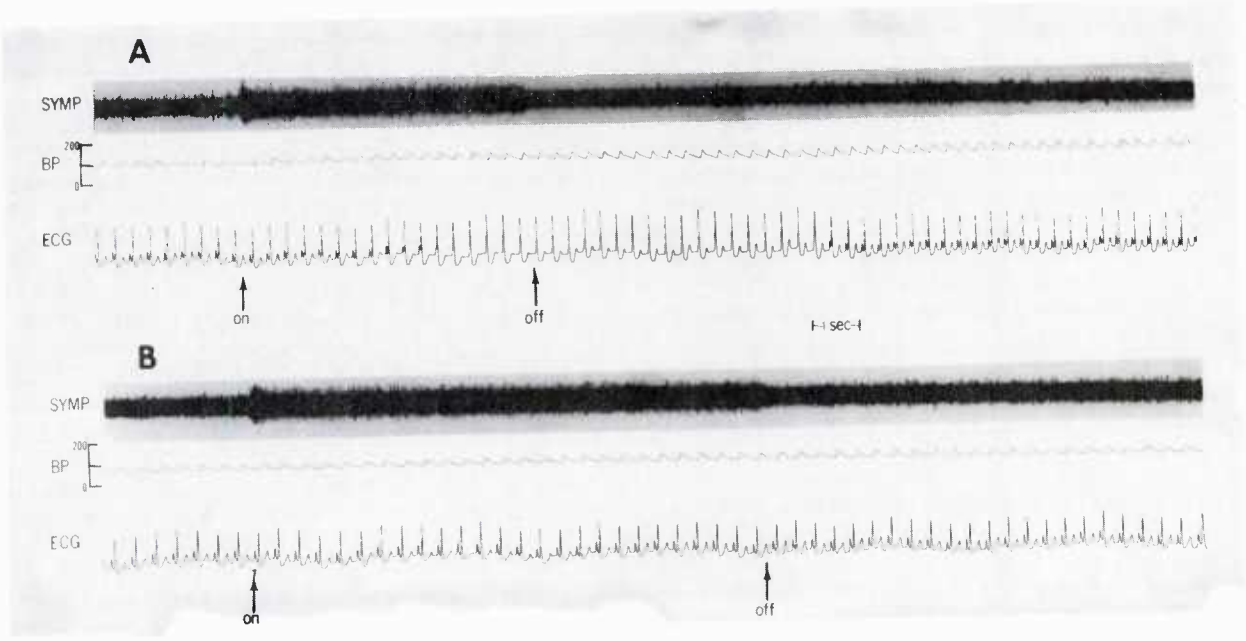

Figure 5. Effect of lidocaine on sympathetic nerve activity (SYMP), cardiac rate and rhythm (ECG), and arterial blood pressure (BP) responses produced by electrical stimulation of the posterior hypothalamus (as indicated by arrows). Panel A shows control recordings. Panel B shows recordings made 2 minutes after I.V. administration of 4.0 mg/kg of lidocaine.

The changes in cardiovascular parameters and integrated nerve activity which occurred in the four experiments with stimulation of the posterior hypothalamus before and after lidocaine are summarized in Table III. Significant increases in mean blood pressure, heart rate, and nerve activity occurred with hypothalamic stimulation prior to lidocaine administration. No significant increases in mean blood pressure or heart rate occurred with hypothalamic stimulation after lidocaine administration. On the other hand, the increase in nerve activity which occurred during stimulation was not affected by pretreatment with lidocaine. In addition, as mentioned above, arrhythmias were observed in each animal with stimulation before lidocaine but never occurred with stimulation after lidocaine. Finally, pretreatment with lidocaine produced significant reductions in the base mean blood pressure but had no significant effect on heart rate or the spontaneous discharge occurring in sympathetic nerves.

Table III. Effect of Lidocaine on Cardiovascular Responses and Sympathetic Nerve Activity Changes Induced by Stimulation of the Posterior Hypothalamus*

Experimental condition	Initial			Maximal changes induced by hypothalamic stimulation		
	Mean blood pressure (torr)	Heart rate (beats/min)	Nerve activity (mm)	Mean blood pressure (torr)	Heart rate (beats/min)	Nerve activity (percent change)
Responses obtained before administration of lidocaine	133 ± 13.4	142 ± 15.2	14 ± 0.9	+25 ± 9.6†	+15 ± 3.1†	+63 ± 11.7†
Responses obtained after administration of lidocaine	95 ± 5.7	121 ± 11.2	15 ± 3.4	+15 ± 6.6	+4 ± 3.7	+62 ± 14.7†
Difference of values obtained before and values obtained after lidocaine administration	-37 ± 8.7‡	-21 ± 7.4	+0.4 ± 2.6	-10 ± 8.5	-11 ± 6.4	-0.8 ± 23.7

* Data obtained from four animals. Values are the mean ± S.E.
† $p < 0.5$ with paired comparisons between values obtained before and values obtained during hypothalamic stimulation
‡ $p < 0.5$ with paired comparisons between values obtained before and values obtained after lidocaine administration

Lidocaine was also tested against arrhythmias induced by peripheral sympathetic nerve stimulation in four experiments. In contrast to diphenylhydantoin, administration of lidocaine (5.2 ± 1.10 mg/kg) prevented the sympathetic arrhythmia induced by peripheral nerve stimulation. This occurred in four of four experiments and a representative example appears in Figure 6.

Lidocaine was also studied in four animals to determine whether or not it would modify the positive chronotropic effects of norepinephrine. Doses of lidocaine tested ranged from 10 to 12 mg/kg (average of 11.5) and were chosen because these doses would have definitely produced blockade of the peripherally induced arrhythmia. Before lidocaine administration, norepinephrine in doses of 1, 3 and 10 μg/kg increased heart rate by 23.2 ± 6.5, 29.2 ± 4.3, and 47.0 ± 11.0 beats/minute, respectively. After lidocaine administration, these same doses of norepinephrine increased heart rate by 25.8 ± 8.1, 35.0 ± 9.0, and 44.2 ± 9.2 beats/minute, respectively. Hence, lidocaine had no significant effect on sinus tachycardia evoked by intravenous norepinephrine.

The results with lidocaine suggested that this drug blocked the centrally induced sympathetic arrhythmia by a peripheral rather than a central mechanism. To obtain further information on this point, studies identical to those performed with lidocaine were carried out with methyllidocaine, a quaternary derivative of lidocaine. This agent penetrates the blood-brain barrier poorly and hence should be devoid of significant actions in the central nervous system. Administration of methyllidocaine (average of 3.7 ± 0.90 mg/kg) to three animals prevented the occurrence of the arrhythmias induced by posterior hypothalamic stimulation. A representative experiment is presented in Figure 7.

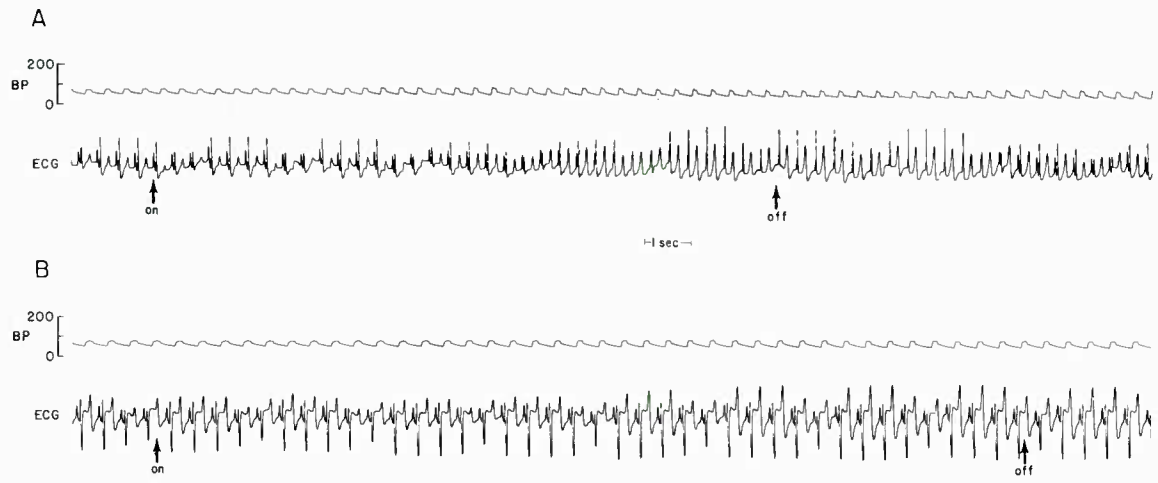

Figure 6. Effect of lidocaine on the cardiac rate and rhythm (ECG) and arterial blood pressure (BP) responses produced by electrical stimulation of the left cardiac sympathetic nerves (as indicated by the arrows). Panel A shows control recordings. Panel B shows recordings made 2 minutes after I.V. administration of 4.0 mg/kg of lidocaine.

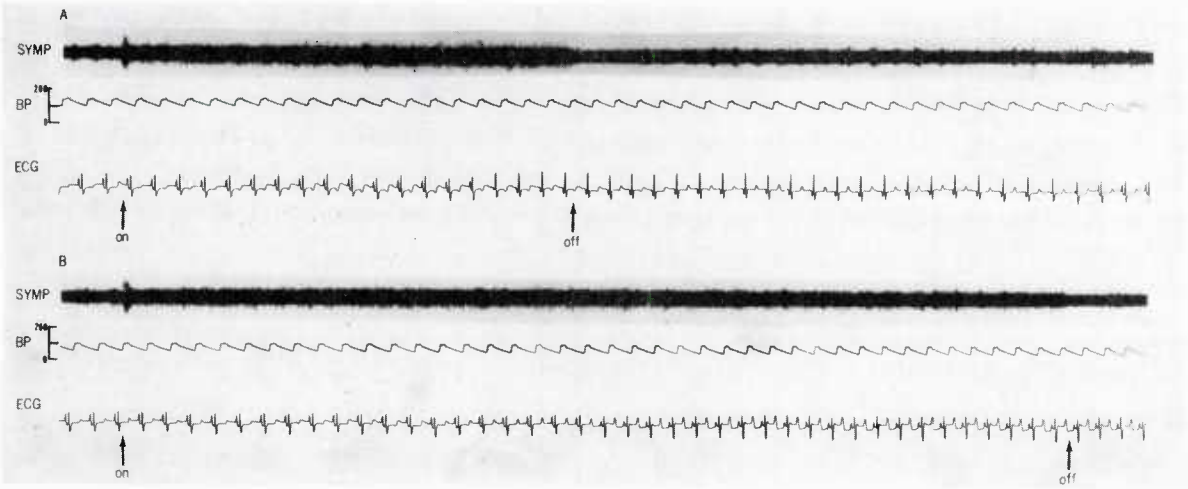

Figure 7. Effect of methyllidocaine on sympathetic nerve activity (SYMP), cardiac rhythm (ECG), and arterial blood pressure (BP) responses produced by electrical stimulation of the posterior hypothalamus (as indicated by arrows). Panel A shows control recordings. Panel B shows recordings made 2 minutes after I.V. administration of 2 mg/kg of methyllidocaine.

As with lidocaine, methyllidocaine was tested for its ability to influence arrhythmias induced by peripheral sympathetic nerve stimulation (three experiments) and heart rate increases induced by intravenously administered norepinephrine (three experiments). Like lidocaine, methyllidocaine prevented the arrhythmia induced by peripheral sympathetic nerve stimulation in each of three experiments but did not modify the heart rate increase induced by intravenous norepinephrine.

IV. DISCUSSION

The purpose of our study was to determine whether or not a neurodepressant action is the mechanism whereby diphenylhydantoin and lidocaine exert their antiarrhythmic effect. To do this we developed a model for studying the effect of these drugs on neurogenic cardiac arrhythmias. The arrhythmia was produced by hypothalamic stimulation and was characterized by a progressive narrowing of the P-R interval until the P wave disappeared and a nodal rhythm predominated. This type of rhythm is termed isorhythmic dissociation.[14,23] Pick[19] has listed the causes of dissociation as: (1) slowing of the primary pacemaker, (2) acceleration of subsidiary pacemakers, (3) A-V block, or (4) a combination of the above factors. In our experiments the isorhythmic dissociation appeared to be the result of an acceleration of A-V nodal pacemakers because no slowing in sinus rate occurred, and no evidence of A-V block was seen. This conclusion is further supported by the fact that the nodal rhythm was always faster than the sinus rate.

The arrhythmia was further characterized by using procedures to determine which division of the autonomic nervous system mediated the response. Procedures employed were pretreatment with propantheline and propranolol as well as bilateral

cervical vagotomy. Results clearly demonstrated that the rhythm disturbance was mediated by sympathetic nerves. Arrhythmias similar to those produced with brain stimulation in the present study have been reported by Korteweg and colleagues.[10] They also observed rhythm changes during stimulation of the posterior hypothalamus of cats characterized by successive shortening of the P-R interval leading to a dominant nodal pacemaker. The authors stated that the arrhythmia could only occasionally be evoked by hypothalamic stimulation. In addition, these investigators found that bilateral vagotomy did not prevent the occurrence of this arrhythmia, suggesting sympathetic mediation.

Since the arrhythmias in the present study were shown to be mediated by the sympathetic nervous system, recordings from the preganglionic sympathetic trunk were used to determine whether a drug was exerting a central neurodepressant action in preventing the neurogenic arrhythmia. Evidence of a central neurodepressant site of action of an antiarrhythmic drug was attenuation of neural hyperactivity at the same time and at the same dose as prevention of the arrhythmia. Evidence of a peripheral neural or cardiac action of a drug was prevention of the arrhythmias induced by peripheral sympathetic stimulation in the absence of a functional central nervous system.

Using these criteria, our results indicate that the antiarrhythmic action of diphenylhydantoin against neurogenic arrhythmias is due to a central nervous system depressive effect and not due to either a peripheral neural depressive effect or a direct cardiac effect of the drug. This conclusion is based on the finding that diphenylhydantoin administration prevented arrhythmias induced by electrical stimulation of the posterior hypothalamus. Doses of drug which were effective in preventing the arrhythmias were

also effective in preventing the autonomic neural hyperactivity responsible for the arrhythmias. In fact, the two effects of the drug were inseparable. Doses of the drug which were inadequate for preventing arrhythmias were inadequate for producing significant depression of sympathetic nerve activity. Furthermore, in no case was the arrhythmia prevented without a significant depression of sympathetic nerve activity. The conclusion is also based on the finding that arrhythmias produced by electrical stimulation of peripheral sympathetic nerves were not prevented by diphenylhydantoin even in high doses. This is important evidence because it suggests that a peripheral nerve site as well as a direct cardiac site was not the responsible site of drug interaction in preventing the arrhythmia. In addition to the above evidence indicating a central nervous system site of action for diphenylhydantoin, we also observed that administration of this agent prevented the occurrence of other changes in cardiovascular function that reflect excessive neural activity. An example of this was the finding that the drug antagonized the increases in heart rate and blood pressure that were associated with posterior hypothalamic stimulation.

Our conclusion that the antiarrhythmic actions of diphenylhydantoin are related to its central neurodepressant properties is in agreement with studies of other investigators. Hockman et al.[8] reached a similar conclusion after observing that diphenylhydantoin antagonized arrhythmias induced by electrical stimulation of the hypothalamus and reticular formation. Ling et al.[12] found that microinjections of diphenylhydantoin into the hypothalamus and reticular formation prevented arrhythmias induced by electrical stimulation of these sites. Roberts[22] obtained data suggestive of a neurodepressant action of diphenylhydantoin but the evidence dealt with the ability of the drug to

depress peripheral adrenergic nervous activity. He observed that antiarrhythmic doses of diphenylhydantoin (10 and 20 mg/kg) significantly reduced the sinus tachycardia evoked by electrical stimulation of preganglionic and postganglionic cardiac sympathetic nerves in cats. He also showed that the same doses of diphenylhydantoin did not significantly reduce the tachycardia induced by intravenous isoproterenol. Roberts concluded that part of the antiarrhythmic action of diphenylhydantoin was related to its ability to depress peripheral adrenergic nervous activity. His results are at odds with ours as we found that peripheral neurodepressant effects of diphenylhydantoin are not in themselves adequate to prevent arrhythmias due to sympathetic hyperactivity. Arrhythmias produced by peripheral sympathetic stimulation in spinal cats (thus excluding central action of diphenylhydantoin) were not prevented by diphenylhydantoin, even in high doses (40 mg/kg).

Unlike diphenylhydantoin, lidocaine did not exert central nervous system depressant actions. Blockade of arrhythmias induced by posterior hypothalamic stimulation occurred but the blockade was not associated with depression of hyperactivity in cardiac sympathetic nerves. These results suggest that lidocaine prevented sympathetically mediated arrhythmias by an action on peripheral sympathetic nerves or on the heart. This conclusion is further supported by the fact that the dose of lidocaine required to prevent arrhythmias induced by peripheral sympathetic stimulation (5.2 ± 1.1 mg/kg) was similar to the dose of lidocaine required to prevent arrhythmias resulting from hypothalamic stimulation (4.0 ± 0.8 mg/kg). However, lidocaine in higher doses (10-12 mg/kg) did not alter the positive chronotropic response to injected norepinephrine, suggesting that lidocaine did not alter the response of the heart to sympathetic influences.

In support of the evidence that lidocaine interacts with peripheral neural mechanisms rather than central neural mechanisms are the findings with methyllidocaine. This derivative of lidocaine would not find access to the brain as it is ionized at body pH and thus would penetrate the blood-brain barrier with great difficulty. This agent was found to block the arrhythmia evoked by posterior hypothalamic stimulation without altering the concomitant changes in sympathetic nerve activity. Methyllidocaine also prevented arrhythmias induced by peripheral sympathetic nerve stimulation but did not alter the increase in heart rate evoked by intravenous norepinephrine. The fact that both centrally and peripherally induced sympathetic arrhythmias were prevented reinforces the conclusion that the antiarrhythmic site of action of both lidocaine and methyllidocaine does not reside in the central nervous system. Similarities between the action of lidocaine and methyllidocaine have been previously reported. Oppenheim[17] demonstrated that methyllidocaine exerts an identical degree of local anesthetic activity as lidocaine, and Oppenheim and Raines[18] and Gillis et al.[6] have shown that the antiarrhythmic effects of the two drugs are similar. However, methyllidocaine does not produce the convulsive effects with lidocaine.

Further support for an antiarrhythmic effect of lidocaine on peripheral cardiac nerves is found in a study by Armour et al.[2] These authors produced a variety of arrhythmias including supraventricular and ventricular tachycardias by electrical stimulation of distal portions of individual cardiac nerves. The arrhythmias were reversibly prevented by either local application of lidocaine to the terminal nerves or by intravenous administration (0.5 mg/kg) of the drug. The authors concluded that the antiarrhythmic effects of lidocaine may be related to its local action on cardiac autonomic

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rule out a myocardial site of action of lidocaine.

Our results also do not rule out a myocardial site of action of lidocaine. We did find that lidocaine had no effect on the increases in sinus node automaticity induced by injected norepinephrine. We assumed that this test would reflect changes, if any, in the response of subatrial pacemakers to norepinephrine. Whether or not one can use responses of the normal pacemaker to sympathetic stimuli and extrapolate the findings to make predictions of the effects of drugs on responses of abnormal pacemakers to sympathetic stimuli has not been established. In summary, while the present studies have not excluded the heart as the site of antiarrhythmic action of lidocaine, our results suggest that peripheral neurodepression may explain its antiarrhythmic effects against arrhythmias caused by neural hyperexcitability.

The data from the present study provide a basis for considering the combined use of diphenylhydantoin and lidocaine for the therapy of arrhythmias. Until now, it has been assumed that these two drugs act at the same site and produce the same electrophysiological effects.[9] Our study indicates that this assumption may not be true because the drugs exert their effects at different sites. Thus more effective therapy for arrhythmias with less dose of each drug may be achieved by the combined use of the two drugs.

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13. ABSTRACT

The importance of the central nervous system in the antiarrhythmic actions of diphenylhydantoin and lidocaine was studied using arrhythmias induced by electrical stimulation of the posterior hypothalamus in cats. Hypothalamic stimulation resulted in cardiac arrhythmias mediated by the sympathetic nervous system. The arrhythmias occurred during stimulation, and recordings from cardiac sympathetic nerves revealed a continuous pattern of hyperactivity during the time of the arrhythmia. Administration of diphenylhydantoin (10-15 mg/kg I.V.) prevented both the arrhythmias and the hyperactivity in sympathetic nerves. Diphenylhydantoin had no effect on similar arrhythmias evoked by electrical stimulation of peripheral sympathetic nerves. Administration of lidocaine (2-6 mg/kg I.V.) prevented the arrhythmias produced by hypothalamic stimulation without attenuating sympathetic hyperactivity, and also prevented similar arrhythmias produced by stimulation of peripheral sympathetic nerves. Results identical to those obtained with lidocaine were observed with methyllidocaine, a quaternary derivative of lidocaine that does not easily penetrate the blood-brain barrier.

These results suggest that the antiarrhythmic action of diphenylhydantoin against neurogenic arrhythmias is due to its central neurodepressant action. The results further suggest that, in contrast to diphenylhydantoin, lidocaine acts at peripheral neural or cardiac sites to antagonize neurogenic arrhythmias.

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