Effects of Sodium Pentobarbital on Electrical and Reflex Activation of the Cardiovascular System

By Clarence N. Peiss, Ph.D., and John W. Manning, Ph.D.

The effects of barbiturates on the cardiovascular system have been reported by many investigators. These effects include reduction of vagal inhibition of the heart rate, direct myocardial depression, and depression of pressor responses to sciatic nerve stimulation. Bouckaert and Heymans reported that the carotid sinus reflex in dogs is depressed by barbiturates. Several investigators have concluded that these anesthetic agents have a significant effect on central neural mediation of cardiovascular reflexes. Masserman showed that sympathetic responses to faradic stimulation of the hypothalamus in the cat are markedly decreased by sodium Amytal in doses of 20 to 50 mg/kg. He also demonstrated a decrease in blood pressure when small amounts of this drug were injected directly into the hypothalamus. Similar results were reported by Dikshit, who also demonstrated depression of chloroform-induced arrhythmias by barbiturates. Redgate and Gellhorn reported that injection of sodium thiopental into the posterior hypothalamus of cats produced a fall in blood pressure and heart rate, with recovery to control levels occurring 25 to 30 minutes later. Reduction of pressor responses and reversal to depressor responses during electrical stimulation of the brain stem was shown recently by Gutman et al. Peiss suggested a hypothalamic site of action for the depressant effects of pentobarbital on cardiovascular responses in the cat. Since it is known that large doses of barbiturates have direct myocardial actions, much of the previous work is subject to question in relation to specific site(s) of action of these compounds. Even the microinjection results are inconclusive due to possible neural effects of tissue compression, pH, etc. It is known that pentobarbital in small doses blocks ascending somatic afferents in the reticular formation and depresses evoked potentials in the thalamus and hypothalamus. Bradley has shown that the minimum dose of sodium pentobarbital which causes elevation of the threshold for both behavioral and EEG arousal is 3.5 mg/kg. It is the purpose of this paper, therefore, to describe experiments illustrating differential effects of small doses of sodium pentobarbital on central nervous structures mediating cardiovascular reflexes in dogs, under conditions in which peripheral cardiovascular effector status can be assessed.

Methods

Experiments were carried out on 22 adult mongrel dogs weighing between 8.1 and 10.5 kg. Dogs were selected for size and head shape in order to minimize variations in stereotaxic placement of electrodes. The animals were given 2 mg/kg of phencyclidine hydrochloride (Sernylan *) intramuscularly. Alpha-chloralose was then administered intravenously until the first sign of pupillary constriction was observed (80 to 80 mg/kg). Bilateral cervical vagotomy was performed in order to confine short-latency heart rate changes to those mediated by sympathetic outflow, and to eliminate compensatory vagal reflex effects on the heart. All animals were ventilated with intermittent positive pressure. In all experiments sodium pentobarbital was injected into the femoral vein at a dose of 5 mg/kg. At the termination of the experiments the brains were fixed with formalin, sectioned, and stained for determination of electrode locations.

* Generously supplied by Parke, Davis and Company.
STELLATE STIMULATION
The chest was opened in the midsternal line and electrodes placed around each stellate ganglion at the caudal pole. Stimulation parameters were: 1.5 to 3.0 v, 5 msec pulse duration, and 10 cycles/sec, using a Grass S4 stimulator.

SCIATIC NERVE STIMULATION
The sciatic nerve was dissected free for a length of two inches. It was then sectioned and
secured with a ligature to a stand in such a way that it was free of adjacent muscle. Bipolar platinum electrodes were placed on the proximal end and the nerve was covered with mineral oil to prevent drying. Stimulation parameters were: 4 to 8 v, 1 msec pulse duration and 50 cycles/sec.

**CAROTID OCCLUSION**

In some experiments the carotid arteries were exposed with a small midline incision in the neck, and were occluded with artery clamps. In other experiments a long incision was made and the carotid arteries dissected free up to the bifurcation of the internal and external carotids. Umbilical tapes were placed under each common carotid artery just below the bifurcation. In these experiments occlusion was performed with artery clamps and the sinus walls were stretched by pulling caudally on the tapes. Occlusions were maintained for 45 to 60 seconds.

**STIMULATION OF MEDULLA AND HYPOTHALAMUS**

After making skin incisions in convenient locations on the skull, the muscles were retracted from the skull and the periosteum scraped off with a surgical chisel. Small bur holes were made with an osteological drill mounted in the stereotaxic carrier. Bipolar concentric electrodes were positioned under stereotaxic control in the posterior hypothalamus (R16-19, RL or LL1-3 and H6-10) and in the dorsal reticular formation of the medulla (C4-7, RL or LL 3 and H5-8). Stimulation parameters were: 1.3 to 4.2 v, 2 msec pulse duration and 100 cycles/sec.

**RECORDINGS**

Blood pressure was recorded from the abdominal aorta via a large catheter inserted into the femoral artery. The catheter was connected to a Statham P23Db pressure transducer through a 1" 22-gauge needle for critical damping of the transducer response. Heart rate was registered continuously by an integrating cardiotachometer. In 10 animals myocardial force was recorded with a Walton strain gauge arch sutured to the left ventricle. All recordings were made on a Midwest model 501 oscillograph using galvanometers with a flat frequency response of 180 cycles/sec. The recorded signals were simultaneously monitored on a Rycom 17" oscilloscope. Electrical stimulation parameters were adjusted to produce a moderate but far from maximal response.

**Results**

Figure 1 is a composite photograph of original recordings showing the effects of 5 mg/kg sodium pentobarbital on the cardiovascular responses to electrical stimulation of the hypothalamus, medulla and right stellate ganglion. The control record (A) shows a typical response to stimulation of the posterior hypothalamus, with striking increases in blood pressure, heart rate, and myocardial contractility, all of which were markedly reduced when the identical stimulus was applied five minutes after administration of sodium pentobarbital (B). Both systolic and diastolic pressure responses to hypothalamic stimulation were reduced after pentobarbital, but the effect on systolic pressure was greater.

The middle portion of figure 1 shows a moderate depression of cardiovascular responses to stimulation of the dorsal medullary reticular formation after administration of pentobarbital. There was no reduction in the response of diastolic pressure to medullary stimulation in this dog. In other experiments in which lower intensities of stimulation were used, reversal of pressor to depressor responses has been noted from both hypothalamus and medulla. This confirms the recent report of Gutman et al. The bottom segment of figure 1 indicates that sodium pentobarbital had no significant effect on cardiovascular responses to electrical stimulation of the right stellate ganglion. At this dosage, therefore, sodium pentobarbital does not appear to have direct effects on the peripheral sympathetic system or the myocardium itself. In all of the above experimental procedures it was possible to override the depressant effects of the pentobarbital by increasing stimulation intensity. For this reason it is imperative that stimulation voltages be constantly monitored by oscilloscope.

Table 1 summarizes the data for stimulation of these three structures in all animals. At least two, and usually three, stimulations of each area were performed before and after administration of the pentobarbital. Values in table 1 are the average response of all stimulations in all animals. The P values in the right hand column indicate that the effects of sodium pentobarbital on heart rate, blood pressure and diastolic pressure were significant for both medulla and hypothalamus. There was no significant difference in responses to stel-
TABLE 1
Effect of Sodium Pentobarbital (5 mg/kg) on Cardiovascular Responses to Stimulation of Hypothalamus, Medulla and Stellate Ganglion

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Changes in heart rate</th>
<th>Changes in pulse pressure</th>
<th>Changes in diastolic pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before pentobarbital</td>
<td>After pentobarbital</td>
<td>% decrease after</td>
</tr>
<tr>
<td></td>
<td>beats/min</td>
<td>beats/min</td>
<td></td>
</tr>
<tr>
<td>hypothalamus (12)</td>
<td>161</td>
<td>208</td>
<td>47</td>
</tr>
<tr>
<td>medulla (10)</td>
<td>157</td>
<td>197</td>
<td>40</td>
</tr>
<tr>
<td>stellate (10)</td>
<td>156</td>
<td>197</td>
<td>41</td>
</tr>
</tbody>
</table>

Figures in parentheses indicate number of animals in each group.
Cont. = control; Stim. = during stimulation; Incr. = increment.

late stimulation after the pentobarbital. Pentobarbital depression of hypothalamic responses in the three cardiovascular parameters shown in table 1 was significantly greater than depression of medullary responses (P = 0.001).

Although responses to stimulation of the stellate ganglia remain undiminished after administration of 5 mg/kg of sodium pentobarbital, a depressant effect occurred when doses of 10 mg/kg were used in a series of six animals. It has also been noticed that smaller doses will cause depression of responses to stellate stimulation if administered to an open chest animal after several hours of experimentation.

The data on pulse pressure changes were qualitatively confirmed by simultaneous recording with the Walton strain gauge arch. For numerous reasons, however, it does not appear to be valid to attempt quantitation of the latter measurement.

Figure 2 illustrates the results of reflex
activation of cardiovascular responses by stimulation of the sciatic nerve and bilateral carotid artery occlusion before (A) and after (B) intravenous administration of 5 mg/kg sodium pentobarbital. In the top segments of this figure the solid line represents the total time during which both carotid arteries were occluded. At the arrow S, with occlusion maintained, the carotid sinuses were stretched by pulling up on the tapes which had been placed around them. The stretch was maintained until the arrow R, at which time it was released. A marked depression of the responses in heart rate, pulse pressure, and diastolic pressure occurred after pentobarbital. It is difficult to determine, however, whether the inhibitory response to stretching of the sinus walls was affected by the drug. Other experiments have shown that there is not a marked effect of this drug on sympathetic inhibitory responses elicited by stimulation in the anterior hypothalamus and preoptic region.

The lower segments of figure 2 show the results of stimulation of the proximal sciatic nerve. A small pressor and augmentor response was elicited, with a negligible response in heart rate. After pentobarbital most of the pressor and augmentor response was eliminated and a decrease in heart rate was observed. Since the animal was bilaterally vagotomized, this decrease in heart rate must presumably have been mediated by central inhibition of sympathetic outflow to the heart. The decreased heart rate resulting from sciatic nerve stimulation after pentobarbital was not abolished by atropine.

In another series of control studies it was shown that additional doses of Sernylan (1 mg/kg) or chloralose (30 mg/kg) did not
cause depression of these reflexly induced cardiovascular responses.

Table 2 is a summary of data for carotid occlusion and sciatic nerve stimulation experiments. Changes in response to sciatic nerve stimulation after pentobarbital were significantly different from control responses. \( P \) values for carotid occlusion experiments, however, were between 0.05 and 0.02. This is due to a wide variance in response from animal to animal, which is discussed below.

**Discussion**

The use of stimulation of the stellate ganglia in these experiments provides a measurement of the effects of sodium pentobarbital on all structures from the preganglionic fiber out to and including the cardiac effectors. The data support the conclusion that small doses of this drug have effects in several parts of the central nervous system involved in cardiovascular regulation. These experiments do not assess possible actions of sodium pentobarbital on spinal interneural or preganglionic cells. It is conceivable that depression of responses to stimulation of the posterior hypothalamus and dorsal medullary reticular formation may be due to drug effects at these sites. However, under these conditions one would not expect the marked difference in pentobarbital depression between these two areas in the brain. Together with other evidence in the literature, the data support the conclusion that, at small dosages, sodium pentobarbital has significantly more depressant effect on the hypothalamus than on the medulla. It is of interest to note that the sensitivity of these two areas to \( d \)-tubocurarine is just the reverse.\(^{17} \)

Further study is necessary to determine...
whether this depressant action of sodium pentobarbital on central structures mediating cardiovascular reflexes is comparable or perhaps even more pronounced at higher levels of the central nervous system. Comparative studies of this type, dealing with the limbic system and cerebral cortex, have not been performed. It is known, however, that dogs under pentobarbital anesthesia yield many more depressor responses to electrical stimulation of the sigmoid gyri than dogs under ether. 18

Sodium pentobarbital also depresses reflex activation of the cardiovascular system as shown in the carotid occlusion and sciatic nerve stimulation experiments. Responses to carotid occlusion in the dog, both before and after pentobarbital, are very variable. In some animals no change in heart rate occurred. In others there was a tremendous cardiac activation involving both acceleration and augmentation. It seems reasonable that the level of sympathetic tone varies widely in these animals, and that therefore the effective stimulus delivered when the carotid arteries are occluded is not constant from animal to animal or even in the same animal from time to time. For these reasons it is felt that the carotid occlusion reflex is not a reproducible test measure unless resort is made to controlled perfusion of the isolated carotid sinuses. The magnitude of the reflex responses in those cardiovascular parameters which were measured, and their per cent depression by pentobarbital, suggest that mediation of these reflex responses in the intact animal is not confined to the medullary vasomotor area. This would support the conclusions of Manning, 19 who demonstrated that massive lesions in the dorsal pontomedullary reticular formation produced only insignificant changes in the responses of this preparation to hypothalamic stimulation and to bilateral carotid occlusion.

Summary

The effects of small doses of sodium pentobarbital (5 mg/kg) on the cardiovascular responses to stimulation of the medulla, hypothalamus, stellate ganglia and sciatic nerve, and to bilateral occlusion of the carotid arteries were studied. It was concluded that: 1) this drug depressed cardiovascular responses to all of these procedures except stimulation of the stellate ganglia; 2) the effects of the anesthetic in this dose are referable to some part(s) of the central nervous system; 3) cardiovascular responses to hypothalamic stimulation were depressed more than those elicited by stimulation of the dorsal medullary reticular formation.

References

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