Chronic Labile Hypertension Produced by Lesions of the Nucleus Tractus Solitarii in the Cat

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SUMMARY
Bilateral electrolytic lesions of the nucleus tractus solitarii (NTS) were made at the level of the obex in seven cats. Within 1 hour the mean arterial pressure (MAP) rose to a maximum of 144 mm Hg (141% of control), and by 7 hours heart rate reached a peak of 236 beats/min (148% of control). The baroreceptor reflexes were abolished. After 24 hours the arterial pressure became extremely labile, with variations of 80-100 mm Hg observed. The lability occurred spontaneously and during behaviors that were self-initiated or elicited by environmental stimuli. The MAP in the lesion group was 144 mm Hg (180% of control) during the day, and 96 mm Hg (120% of control) at night. The lability, measured by the standard deviation, during the day in the lesion group was 4 times greater than in the control group and at night there were no differences. The heart rate of the lesion group was always higher than that of the control group but the lability of both groups was the same. We conclude that lesions of the NTS produced labile hypertension, probably by disinhibition of sympathetic activity through central interruption of the baroreceptor reflexes. The higher, more labile arterial pressures during the day may be caused by uninhibited increases in sympathetic activity elicited by environmental stimuli that are present during the day and absent at night. The daily variation of pressure may also be caused by somatomotor activity or by a daily rhythm of sympathetic activity which is unmasked by the lesions.

THE CENTRAL nervous system may play a critical role in the initiation of and/or maintenance of several models of experimental hypertension in animals1 and possibly of essential hypertension in man.2-4 Neurogenic hypertension may result from an imbalance between systems in the brain which excite or inhibit sympathetic discharge. The imbalance could favor increased sympathetic discharge either by chronic electrical stimulation of the hypothalamus, by producing brain ischemia, by subjecting animals to stress, or by behavioral conditioning.4 Hyper- tension results from these procedures but it lasts, at most, for only a few weeks.

Many attempts to produce animal models of experimental hypertension have aimed at increasing sympathetic discharge either by chronic electrical stimulation of the hypothalamus, by producing brain ischemia, by subjecting animals to stress, or by behavioral conditioning.4 Hyper- tension results from these procedures but it lasts, at most, for only a few weeks.

Other studies have attempted to produce experimental hypertension by withdrawing inhibition of sympathetic discharge by somatomotor activity or by a daily rhythm of sympathetic activity which is unmasked by the lesions.
neurons by denervating the baroreceptors peripherally through transection of the carotid sinus and aortic depressor nerves (sinoaortic denervation). Most investigators are agreed that the procedure produces an increase in the lability or variation of the arterial pressure. However, there has been disagreement about the effect on the mean level of the arterial pressure. The most recent report showed that sinoaortic denervation raised the mean arterial pressure only slightly but, in agreement with earlier reports, the lability of arterial pressure was greatly increased. The increased lability was observed for as long as 1 year after the denervation in this study.

Recently, our laboratory used a new method for producing a model of neurogenic hypertension. The baroreceptor reflexes were interrupted centrally by bilateral placement of electrolytic lesions within the region of the nucleus tractus solitarius (NTS) in rats. This brainstem area is the terminus of many of the afferent fibers of the baroreceptors. Hypertension rapidly developed after placement of the lesions, but it was followed within hours by cardiac failure, pulmonary edema, and death. Thus, while the procedure was successful in producing neurogenic hypertension, the hypertension spanned only a few hours.

The present study was designed to determine whether NTS lesions placed in the cat would abolish the baroreceptor reflexes and produce neurogenic hypertension that would last for a longer period of time than it did in the rat. We report that NTS lesions in the cat produces an elevation in the mean level of arterial pressure and an increase in the lability of the pressure. The arterial pressure was measured for as long as 5 months after placement of the lesions and these effects were continuously present throughout the observation period.

Methods

ANIMALS AND GENERAL PROCEDURES

The experiments were performed on 12 vaccinated, adult cats of both sexes that were instrumented for the recording of cardiovascular activity (see below). Lesions of the NTS were made in seven cats. In three of these cats the instrumentation procedure was performed in a first operation, and 1–2 weeks later NTS lesions were placed in a second operation. In four cats, the placement of NTS lesions and the instrumentation procedure were done at the same time. Sham lesions were made in five cats. In these cats the instrumentation procedure and placement of sham lesions were performed in a single operation. All cats were observed for 1 week to 5 months following the last operation.

At 1–2 days prior to surgery, a prophylactic antibiotic (sterile penicillin G benzathine suspension, 200,000–300,000 U, im) was administered. After induction with ether and tracheal intubation, the cats were maintained with halothane (1–2% in 50% oxygen and 50% nitrogen) delivered through a clinical anesthesia machine. All surgical procedures were performed under aseptic conditions. During surgery, body temperature was maintained at 37°C (±0.5°C) by a rectal probe connected to a thermostatically regulated electric heating pad. The cats were maintained on saline (0.9%, iv) throughout the surgery. All cats, after placement of the NTS lesions or sham lesions, failed to eat or drink, and spontaneous movements were reduced for about 1 week. The cats were therefore maintained on 5% dextrose and water (iv) until they were eating and drinking normally. In other respects the cats were in good health.

IMPLANTATION OF CANNULAS AND ELECTRODES

The right common carotid artery and external jugular vein were exposed by splitting the sternocleidomastoid muscle and retracting the diaphragm. A polyvinyl chloride (PVC) cannula (inner diameter = 0.049 inch) filled with saline containing heparin (50 U/ml) was inserted into the common carotid artery and passed into the thoracic aorta. The venous cannula was threaded through the jugular vein to rest in the right atrium. After fixation to soft tissues, the cannulas were clamped and the free ends were threaded subcutaneously to be brought out through the skin overlying the back of the head. The arterial cannula was threaded through a 13-gauge stainless steel tube cut to a length of 1.5 cm. The tube was oriented vertically to the top of the head and cemented with dental acrylic (Kerr Manufacturing Co.) to the top of the skull. The position of all cannula tips was verified post mortem.

In some cats electrodes were implanted during the instrumentation procedure for recording extraocular movements (EOM), the electroencephalogram (EEG), and the electromyogram (EMG) of neck muscles. The EOM and EEG electrodes were prepared in advance by soldering lengths of Teflon-insulated stainless steel wire (diameter = 0.006 inch) to no. 0 stainless steel machine screws (80 threads per inch, 0.25 inch long). The EEG electrodes were implanted in the superior and inferior orbital ridges and wires were threaded subcutaneously to the top of the head and brought through the skin. A midline incision was made in the skin of the head, and the skull was bare for implantation of the EEG electrodes which were inserted into the skull 1–1.5 cm to either side of the midline overlying the parietal cortex. The EMG electrodes were fashioned from stainless steel wires (diameter = 0.006 inch) insulated with Teflon to within 1.5 cm of the tips. The tips of the electrodes were bent into the shape of hooks. The electrodes were implanted through small skin incisions made over the paravertebral cervical musculature to either side of the midline. Movement artifact was minimized by pulling the electrodes through the muscle until the hooks were firmly anchored in the tissue. The insulated portions of the wires were then passed subcutaneously up the back of the neck and brought out through the head incision next to the other wires. All wires from the electrodes were soldered to a miniature, multipin socket (Augat, part 8058-1G68). The socket was connected to the skull with the dental acrylic.

The arterial cannula was threaded through a flexible spring and one end of the spring was fitted over the metal tube that had been cemented to the skull. After the cat was placed in the cage, the other end of the spring and the cannula were attached to a hydraulic swivel (model 193-03, BRS/LVE, Beltsville, Md.) which was mounted on top of the cage. The spring served to prevent the cannula from...
kinking during movement of the cat. The other end of the swivel was connected by a tube to a strain gauge transducer (Statham, P23Db). The venous cannula was taped to the side of the spring and was connected directly to another transducer (Statham, P23Gb) when venous pressure was recorded. At other times, the end of the venous cannula was sealed and allowed to rotate freely as the cat moved about the cage. Arterial and venous pressures were displayed on a Beckman polygraph (type RM). The peak of the arterial pressure pulse was used to trigger a cardiotachometer (Beckman 9857) and the heart rate was simultaneously displayed. Mean arterial blood pressure (MAP) was computed by an electronic averaging circuit (time constant = 0.53 second). Corrections were made to compensate for the difference in the heights of the recording transducers and the level of the heart. The cannulas were kept open by periodic flushing with heparinized saline.

**PLACEMENT OF NTS LESIONS**

The cats were placed in a stereotaxic frame with the head flexed to 45°. The atlantoccipital membrane was visualized by separation of the posterior muscles of the neck in the midline. The dura overlying the foramen magnum was incised and the region of the obex was exposed. In most of the cats, a small portion of the posterior vermis of the cerebellum was removed by gentle suction in order to visualize the floor of the 4th ventricle.

The electrodes used for placement of the lesions in the NTS consisted of a Teflon-coated stainless steel wire (diameter = 0.006 inch) insulated to within 0.4 mm of the tip and carried in a 28-gauge stainless steel hypodermic tubing. Bilateral lesions were placed in the NTS at levels 0.5 mm caudal and 0.5 mm rostral to the obex; along the medial side of the posteroventral sulcus and at a depth of 1.0–1.5 mm beneath the floor of the 4th ventricle. The lesions were made by passing a DC anodal current of 5 mA for 15–30 seconds. The cathode was a clip attached to the adjacent neck muscle. The control cats were operated in the same way as the cats with NTS lesions. The floor of the 4th ventricle was exposed and the posterior vermis of the cerebellum was aspirated. In one control, electrodes were inserted into the NTS but the current was not passed. The operation was completed by closure of the neck incision and discontinuation of the halothane. The cats were returned to their cages and recording of cardiovascular activity was begun.

**ENVIRONMENTAL CONDITIONS**

The cats were housed in cages (67.5 cm wide x 60 cm high x 55 cm deep) that were constructed of wooden walls, a wire-mesh floor, and a door made of clear plexiglass. The cages were placed on benches in a large, busy laboratory. No special attempts were made to shield the cats from ambient visual or auditory stimuli.

**CONSTRUCTION OF FREQUENCY HISTOGRAMS**

Lability of arterial blood pressure and heart rate was assessed by use of frequency distribution curves that showed the number of times that a variable assumed a certain value during a selected time period. The curves were constructed by visually determining from the polygraph records the average systolic, diastolic, MAP, and the heart rate during every minute over a selected 1-hour period. The entire range of arterial pressures and heart rates then was divided into intervals of 5 mm Hg or 5 beats/min and the frequencies at which the various values of arterial pressures or heart rates fell within each interval were tabulated. The reciprocals of the frequencies times 100 were plotted as percentages on the graphs of the frequency histograms.

**STATISTICAL EVALUATION**

Means and standard deviations were used to summarize the frequency distributions from each cat. The means describe the average of the MAP and heart rate, and the standard deviations describe the lability of these variables within each distribution. Group statistics were computed by averaging the means, and the standard deviations from all the cats belonging to the same group. The significance of changes in the cardiovascular responses resulting from brain lesions was determined by two-tailed t-tests. Changes were considered to be significant at \( P < 0.05 \).

**BEHAVIORAL OBSERVATIONS**

To determine the effects of NTS lesions on the changes in arterial blood pressure and heart rate during different behaviors, the cats were observed while cardiovascular activity was being recorded. The changes in arterial pressure and heart rate was assessed during the following behaviors: grooming, feeding, changes in posture, orienting (elicited by an unexpected tapping sound on the front of the cat's cage), and rapid eye movement (REM) phase of sleep.

**HISTOLOGICAL EXAMINATION**

The cats were killed by an intravenous injection of sodium pentobarbital (35–40 mg/kg). The brain was perfused with normal saline followed by 10% formalin. The brain was removed and placed in 10% formalin for at least 2 weeks. The localization of brain lesions was confirmed on frozen sections cut every 50 μm and stained for cells by the Nissl method. Obstruction of vessels within the lungs and kidneys by thrombi formed at the tips of the arterial and venous cannulas was assessed in three cats. No infarcts were observed.

**Results**

**ACUTE PHASE**

**Arterial Blood Pressure**

Within 15 minutes after placement of bilateral electrolytic lesions in the NTS and termination of the anesthetic, the systolic and diastolic pressures and the MAP began to rise in all cats. Average response levels for the NTS group are shown in Figure 1. The MAP rose to a maximum of 144 mm Hg at 1 hour; this was significantly higher than that of the control group. Coincident with a decline of the average level of arterial pressure was the gradual appearance of intermittent, spontaneous fluctuations of the arterial pressure. These were seen by the 4th to 8th postopera-
HYPERTENSION INDUCED BY CNS LESIONS/Nathan and Reis

HALOTHANE

140

8120

100

5

240

180

5

150

°

UJ n

O 0

2 3 4 5

TIME (hrs)

FIGURE 1 Effect of lesions of the nucleus tractus solitarii (NTS) during the acute phase on the mean arterial blood pressure (A), heart rate (B), and central venous pressure (C) of a group of cats. All cats were anesthetized for the period of time indicated by the shaded area. The data points on the left edge of the shaded area represent the responses recorded 1 hour before placement of lesions. The data points on the right edge of the shaded area represent the responses in the experimental group (filled circles, n = 6) after placement of NTS lesions or in the control group (open circles, n = 7) after sham lesions. At time 0, the anesthesia was stopped and the time course of cardiovascular activity for the next 8 hours was followed. Each data point signifies a mean value and the bars indicate ±SE. The significance of differences from the control at each time point is represented by asterisks: *P < 0.05; **P < 0.01; ***P < 0.001.

tive hour and gradually increased in frequency, duration, and magnitude. By 24 hours lability of the arterial pressure was pronounced.

Heart Rate

The lesions also resulted in a significant elevation in heart rate (Fig. 1). The average heart rate increased more slowly than the MAP, reaching a maximum average level of 236 beats/min at 7 hours after cessation of the anesthesia.

Venous Pressure

The venous pressure was unchanged following NTS lesions in all surviving cats (Fig. 1). In one cat, not included in the study, the venous pressure was substantially elevated. This cat died with pulmonary edema.

Respiration

Respiration ceased in two of the cats after placement of the lesions. These cats were mechanically ventilated 20-45 minutes before spontaneous respiration resumed. One of these cats and two others developed apneusis. After 1-2 hours, however, all cats were breathing normally.

CHRONIC PHASE

By 24 hours after the surgery, the cats with NTS lesions developed marked lability of the arterial pressure (Fig. 2). The lability was striking and included elevations, as well as falls, of arterial pressure that were sometimes as great as 100 mm Hg. In some instances the lability seemed to occur spontaneously in that it was not associated with any particular behavior nor with any identifiable stimulus. In other instances the lability was associated with occurrences of spontaneous or evoked behaviors.

The lability of the arterial pressure made it difficult to characterize the response levels over time by the usual method of selecting a few representative data points. We therefore analyzed the data by the generation of frequency histograms. This mode of analysis permitted us to examine the lability graphically and to determine numerically the MAP and standard deviation of each frequency histogram.

Since it appeared from inspection of the chart records that the lability of arterial pressure varied between daytime and nighttime, we analyzed separately the cardiovascular performance of cats at these two times of the day. The lability appeared generally to be greatest during laboratory working hours (8 a.m. to 8 p.m.) and least after closing the laboratory for the day (8 p.m. to 8 a.m.). Therefore, the recordings were segregated into one of the two general categories according to the hour of the day (8 a.m. to 8 p.m.) or night (8 p.m. to 8 a.m.) when the recordings were made. The exact hour of recording was selected to be as close as possible to the midpoint of the daytime or nighttime range (2 p.m. or 2 a.m.).

Arterial Pressure — Daytime

During the daytime there were two changes in arterial pressure in cats with NTS lesions. First, the MAP increased, as indicated by the displacement of the frequency distributions of the cats with the lesions to the right of the distributions of the control cats (Fig. 3A-C). The MAP in the lesion group was 34 mm Hg higher than the MAP of the control group (Table 1A). Second, the lability of the arterial pressure increased markedly as seen by comparing the shapes of the frequency histograms of the cats with the lesions (Fig. 3C) to the distinctly different shapes of the frequency histograms of the control cats (Fig. 3B). In contrast to the prominent peak and narrow range (65-100 mm Hg) of the histograms of the control cats, the histograms of the cats with lesions are flattened and dispersed over 60-170 mm Hg. Numerically the increased lability is indicated by the size of the average standard deviation of the lesion group, which was 4 times greater than the average standard deviation of the control group (Table 1B).
Heart Rate—Daytime

The heart rate was significantly increased during the day in cats with NTS lesions (Fig. 4A-C; Table 1C). While visual comparisons of the frequency histograms of the two groups suggest that the lability of the heart rate was reduced by NTS lesions, the standard deviations of the lesion group did not differ significantly from the control group (Table 1D).

Arterial Pressure—Nighttime

The MAP at night in the cats with NTS lesions was significantly reduced from the daytime levels (Fig. 3D-F; Table 1A). However, it remained significantly elevated in comparison to the control group. The exaggerated lability of the MAP that was seen during the day was not present at night in cats with NTS lesions. Thus, the average standard deviation of these cats and the control cats did not differ significantly (Table 1B).
HYPERTENSION INDUCED BY CNS LESIONS/Nathan and Reis

TABLE I  Effects of Lesions of the Nucleus Tractus Solitarii (NTS) on the Mean Levels of the Mean Arterial Pressure (A) and Heart Rate (C) and the Standard Deviations of the Mean Arterial Pressure (B) and Heart Rate (D) during the Day and Night

<table>
<thead>
<tr>
<th></th>
<th>Day</th>
<th>Night</th>
<th>% difference (night/day)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td><strong>A. Mean arterial pressure (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>80 ± 1.5 (6)</td>
<td>77 ± 3.3 (5)</td>
<td>96</td>
<td>NS</td>
</tr>
<tr>
<td>Lesion</td>
<td>114 ± 2.4 (5)</td>
<td>96 ± 4.7 (4)</td>
<td>84</td>
<td>≤0.02</td>
</tr>
<tr>
<td>% difference (lesion/control)</td>
<td>143</td>
<td>125</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P</td>
<td>≤0.001</td>
<td>≤0.02</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>B. Standard deviation of arterial pressure (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>4 ± 0.4 (6)</td>
<td>5 ± 0.4 (5)</td>
<td>125</td>
<td>NS</td>
</tr>
<tr>
<td>Lesion</td>
<td>18 ± 2.3 (5)</td>
<td>6 ± 0.5 (4)</td>
<td>33</td>
<td>≤0.05</td>
</tr>
<tr>
<td>% difference (lesion/control)</td>
<td>450</td>
<td>120</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P</td>
<td>≤0.001</td>
<td>NS</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>C. Heart rate (beats/min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>154 ± 8.1 (6)</td>
<td>149 ± 6.4 (5)</td>
<td>97</td>
<td>NS</td>
</tr>
<tr>
<td>Lesion</td>
<td>191 ± 5.6 (5)</td>
<td>181 ± 1.4 (4)</td>
<td>95</td>
<td>NS</td>
</tr>
<tr>
<td>% difference (lesion/control)</td>
<td>124</td>
<td>121</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P</td>
<td>≤0.01</td>
<td>≤0.05</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>D. Standard deviation of heart rate (beats/min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>10 ± 1.3 (6)</td>
<td>7 ± 1.2 (5)</td>
<td>70</td>
<td>NS</td>
</tr>
<tr>
<td>Lesion</td>
<td>7 ± 1.7 (5)</td>
<td>7 ± 1.4 (4)</td>
<td>100</td>
<td>NS</td>
</tr>
<tr>
<td>% difference (lesion/control)</td>
<td>70</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>-</td>
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All statistics were computed from the frequency histograms shown in Figures 3 and 4. All values are expressed as means ± se; the number of cats in each group is enclosed in parentheses.
P = significance level; NS = not significant.

Heart Rate—Nighttime

In contrast to the MAP, the average heart rate of cats with NTS lesions seen during the day decreased only slightly at night so that it still remained significantly above the level of the control cats (Fig. 4D–F; Table 1C). The lability was unchanged from that of the control group (Table 1D).

EFFECT OF NTS LESIONS ON THE CARDIOVASCULAR RESPONSES DURING VARIOUS BEHAVIORS

Lesions of the NTS not only increased the range of spontaneous fluctuations of arterial pressure but also greatly exaggerated the normally small fluctuations associated with various behaviors. Thus, the usually small elevation of arterial pressure associated with grooming or ori-
enting were substantially enhanced (Fig. 5). Transient elevations of arterial pressure of up to 100 mm Hg were commonly seen.

NTS lesions also exaggerated naturally occurring reductions in arterial pressure. This was particularly noticeable during the REM phase of sleep. In the normal cat REM sleep is characterized by desynchronization of the EEG, rapid movement of the eyes, relaxation of the muscles of the neck, and a moderate fall of arterial pressure. In cats with NTS lesions, hypotensive responses appeared which frequently reached a level of less than 50 mm Hg and which sometimes remained at the level for several minutes (Fig. 6). The electrophysiological events associated with REM sleep were unaffected by the NTS lesions.

EFFECTS OF NTS LESIONS ON BARORECEPTOR REFLEX ACTIVITY

In all cats, NTS lesions abolished the baroreceptor reflex as demonstrated by the absence of bradycardia after administration of a pressor dose of norepinephrine (Fig. 7).

LESION SITES

In all cats the electrodes were inserted in the NTS 0.5 mm rostral and caudal to the obex. The region of the NTS that was actually destroyed was located between about 1.0 mm rostral and 1.0 mm caudal to the obex. Representative lesions are shown in Figure 8. In some cats the dorsal nucleus of the vagus, the intercalary nucleus, and the medial cuneate nucleus were minimally and variably damaged.

Discussion

ACUTE PHASE

We have shown that bilateral electrolytic lesions of the NTS in cat, as in rat,9 result in the rapid development of arterial hypertension. The acute phase is characterized by stable elevations of arterial pressure of comparable magnitude in both species. However, the effects of NTS lesions on several other variables differed in the cat and rat. First, the cats exhibited a sustained tachycardia which the rats did not develop. Second, the cats generally did not develop elevated venous pressures or other evidence of cardiac failure. All cats, with the one exception previously noted, survived the acute phase after placement of the lesions. The rats, on the other hand, were in failure within 30 minutes after cessation of the anesthesia, with elevated venous blood pressures and left ventricular and diastolic pressures, and reduced cardiac outputs. The rats uniformly succumbed to pulmonary edema after placement of the lesions within 4–6 hours.

The reason the cats survived the acute phase are uncertain. Conceivably, the elevation in heart rate was sufficient to maintain cardiac output, perhaps long enough for other and as yet unidentified compensatory mechanisms to assist in gradually lowering the arterial pressure.

CHRONIC PHASE

Following the acute phase of stable hypertension, cats with bilateral NTS lesions entered the chronic phase consisting of: (1) marked minute to minute lability of arterial pressure; (2) a sustained elevation of MAP during the daytime; (3) exaggerated responsivity of the arterial pressure during various behaviors; and (4) sustained tachycardia.

The explanation accounting for the daily fluctuation in the amount of lability is uncertain but is probably related to interruption of the baroreceptor reflexes by placement of NTS lesions. Conceivably an endogenous, daily rhythm in the activity of sympathetic neurons is, under normal circumstances, buffered by the baroreceptors, and interruption of the baroreceptor reflexes unmasks this rhythm. Alternatively, the fluctuations of arterial pressure could be secondary to changes in somatomotor activity, and after interruption of the baroreceptor reflexes these fluctuations became greatly exaggerated.

Another explanation might be related to the fact that the cats with NTS lesions exhibited an enhanced cardiovascular reactivity to stimulation from their environment.
Since in our study the cats were exposed continuously to the activities of the laboratory in which they were housed, the level of environmental stimulation was greater in the daytime when the laboratory was busy than at night, when it was quiet. In support of this explanation is our observation that the cardiovascular reactivity of the cats with lesions to intentional environmental stimulation, for example, during orienting, was much greater than that of the control cats.

The MAP of the group with NTS lesions was significantly elevated above the level of the control group during the day and the night, whereas the lability of the pressure of the lesion group was significantly greater than the control group only during the day. These two facts suggest that the elevation of the MAP is not merely a statistical artifact caused when computing the mean by the addition of a few extremely high values of arterial pressure to otherwise normal or nearly normal values. Therefore, the sustained increase of the MAP produced by NTS lesions is, at least in part, independent of the increased lability and may reflect an enhanced tonic discharge of vasomotor neurons.

**COMPARISON OF NTS LESIONS AND SINOAORTIC DENERVATION**

The changes in arterial pressure produced by NTS lesions are in all probability due to destruction of the arterial baroreceptor reflex mechanisms within the brain. First, the lesions always destroyed the middle third of the NTS, a major site of integration of arterial baroreceptor reflexes. Second, the reflex bradycardia elicited by elevation of the arterial pressure by norepinephrine was permanently abolished. Third, and indirectly, the disappearance of the major adjustments in cardiac rate in response to large fluctuation of arterial pressure during various behaviors in cats with NTS lesions is entirely consistent with a loss of arterial baroreceptor responses. Since the NTS lesions abolished baroreceptor reflex responses and damaged the first synaptic relay within the brainstem of the fibers that project from the sinus and aortic baroreceptors, the results of NTS lesions and sinoaortic denervation should be compared. However, such comparisons with studies by others are difficult to make because of the differences in species examined, the environment in which the animals were tested, and the methods of data analysis that were utilized. For example, in the only study of the effects of sinoaortic denervation in the unanesthetized cat,
Guazzi and Zanchetti measured the MAP in cats that were isolated from acoustical and visual stimuli. They observed mean levels of arterial pressure that were much lower than the daytime levels measured by us, but comparable to our nighttime levels. The denervated cats also had exaggerated cardiovascular lability during REM sleep. Lability as a variable was not measured.

Lability appears to be a principle effect of sinoaortic denervation in the dog. In a recent study by Cowley et al., analysis of frequency histograms of arterial pressure collected over 24-hour periods from dogs housed in a controlled environment, showed that sinoaortic denervation mainly increased the lability of the pressure and increased the MAP only slightly. Our results show a larger increase in the MAP and in the lability of the arterial pressure.

These comparisons from the literature indicate that sinoaortic denervation and NTS lesions have not only similarities but also differences. Whether such differences are real or an outcome of the variables of species, experimental conditions, and methods of data analysis cannot be established until NTS lesions and sinoaortic denervations are performed in the same species and under comparable conditions.

As a final note, it should be emphasized that there is an important difference between the procedures of sinoaortic denervation and placement of NTS lesions. Although both procedures effectively block baroreceptor activity arising from the carotid sinus and aortic arch, they differ in that the NTS lesions additionally destroy (1) the terminus of baroreceptor afferent fibers that traverse the vagus nerve and which are partially spared by the sinoaortic denervation, (2) the neurons on which the baroreceptor afferent fibers terminate, and (3) projections from other brain areas onto neurons of the NTS. Thus, NTS lesions may be more effective than sinoaortic denervation in increasing the mean level and lability of the arterial pressure.

GENERAL IMPLICATIONS

The present study is the first example of the production of chronic, neurogenic hypertension in an animal model as a consequence of a localized brainstem lesion. The increased lability of the arterial pressure may reflect an imbalance, caused by placement of the lesions, between excitatory and inhibitory systems which modulate sympathetic discharge. Normally, the reciprocal activity of these systems produces an orderly matching of cardiovascular events appropriate to the specific behaviors. After impairment of the inhibitory system by the lesions, an imbalance occurs that favors increased sympathetic discharge. Thus, the relatively small increases in sympathetic activity and arterial pressure normally seen in response to environmental stimulation and during various behaviors are unopposed by baroreceptor activity after NTS lesions, hence the arterial pressure rises to abnormally high levels. When the environmental stimuli are reduced and the behavior ceases, the sympathetic discharge decreases and the arterial pressure returns to more nearly normotensive levels.

Acknowledgments

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HEART PERIOD AND VAGAL EFFECTS ON AV CONDUCTION/Martin

Paradoxical Dynamic Interaction of Heart Period and Vaginal Activity on Atrioventricular Conduction in the Dog

PAUL MARTIN

SUMMARY The dynamic interaction of simultaneously changing heart period and single vagal stimuli on atrioventricular conduction (AV interval) was quantified by subtracting the vagally induced responses of the paced heart preparation from those of the unpaced heart preparation. This difference was significantly greater \((P < 0.05)\) than the AV responses to changes in heart period \((\Delta A)\) alone without vagal stimulation (using the identical \(\Delta A\) recorded from the un-paced heart in the same preparation, but with a crushed sinoatrial node). That is, for a given increase in AA interval, the AV conduction time was considerably less when the change in \(A A\) was associated with increased vagal activity than in the absence of any vagal activity. Data from some dogs in which a complete AV block was produced for both paced and un-paced hearts suggested that one mechanism of the paradoxical response was located in AV nodal tissue. Data from other dogs, in which two surface atrial recording sites were used, indicated that shifts of pacemaker site and atrial activation patterns also are an important mechanism of the paradoxical response. The relative contribution of these two mechanisms is not fixed, but can vary considerably from animal to animal.

IT HAS BEEN SHOWN by us previously that a single stimulus applied to the vagosympathetic trunk of an un-paced dog heart preparation can lead to changes of atrioventricular \((A V)\) conduction time that are extremely complex, with several different mechanisms contributing to the resultant response. \(^1\) Thus, a generalized increase in vagal activity at the sinoatrial (SA) and AV nodes results in two oppositely directed effects on AV conduction time (the AV interval): (1) the acetylcholine \((A C h)\) released will prolong the AV interval via a direct effect on the AV node, and (2) it will indirectly decrease the AV interval by increasing heart period (AA interval), primarily an AV nodal effect. \(^2\) I wished here to define quantitatively the interaction between these two mechanisms. The specific question asked was: Do the two independent effects on AV conduction combine as a simple sum when applied simultaneously, or is there a more complex, nonlinear interaction that produces the resultant response? The second alternative was found to prevail in almost all animals.

The basic protocol used an open-chest, anesthetized dog and consisted of noting the AV conduction responses to the following sequence of experiments: (1) single vagal stimulus bursts delivered at different times throughout the cardiac cycle in the spontaneously beating heart preparation; (2) the identical experiment as above, but with the heart paced at a constant rate just above its spontaneous rate; and (3) with the heart driven at the identical sequence of changing cardiac cycle lengths obtained in part 1 above, but with no vagal stimulation. Thus, the sum of the independent effects of vagal activity and increasing cycle length (parts 2 and 3) can be compared with the response to these combined perturbations (part 1). If the sum of the responses to parts 2 and 3 is significantly different from the responses of part 1, it can be concluded that there is an interaction between these two mechanisms.

Methods

Fifty-five mongrel dogs (10-15 kg) were used, of which 51 yielded satisfactory results. All dogs were anesthetized with morphine sulfate, 2 mg/kg, intramuscularly \((i m)\) followed 30 minutes later by chloralose, 75 mg/kg, intravenously \((i v)\), dissolved in polyethylene glycol. In one group of 44 dogs the chest was opened and bipolar recording catheters were inserted through a small incision in the right atrial appendage into the right atrium, and through the right external jugular vein into the right ventricle. The catheter was lodged against the ventricular wall. The atrial catheter was secured to the atrial appendage just above the proximal electrode \((e l e c t r o d e \ s e p a r a t i o n = 6 \, m m)\), thus eliminating timing errors due to electrode position changes. The electrodes were connected to a Brush Mark 200 oscillograph to record the atrial \((A)\) and ventricular \((V)\) activations. The onset of the atrial potential was the reference event for all other measured, computed, and generated time intervals.

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