Chronic Lability of the Arterial Blood Pressure Produced by Electrolytic Lesions of the Nucleus Tractus Solitarii in the Rat

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SUMMARY. The purpose of this study was to assess the chronic effects of lesions of the nucleus tractus solitarii on the cardiovascular activity of rats. Arterial pressure and heart rate were recorded in conscious, unrestrained rats 7–216 days following placement of electrolytic lesions in the nucleus tractus solitarii. To assess the impact of environmental stimuli on the mean level and lability of the mean arterial pressure, cardiovascular activity was recorded under conditions of controlled and uncontrolled environmental stimulation. Nucleus tractus solitarii lesions abolished the reflex bradycardia to a phenylephrine-induced elevation in arterial pressure. A marked increase in the lability of the mean arterial pressure was produced with nucleus tractus solitarii lesions. The standard deviation of the mean arterial pressure, an index of lability, was 380% greater in rats with lesions than in control rats. The average mean arterial pressure, heart rate and heart rate variability were not significantly different between the lesion and control groups, regardless of the environmental conditions under which the measurements were made. Nucleus tractus solitarii lesions also greatly exaggerated the arterial pressure response to naturally occurring behaviors, such as eating and drinking. Vagal and β-adrenergic blockade with methyl atropine and propranolol did not alter the average level or lability of the mean arterial pressure, although heart rate responses were similar in both groups. α-Receptor blockade with prazosin significantly lowered the mean arterial pressure in both lesion and control rats, but the decrease in mean arterial pressure was significantly greater in rats with nucleus tractus solitarii lesions (42 ± 6 mm Hg, 38.5%) than in control rats (27 ± 4 mm Hg, 23.2%). Prazosin also reduced the lability of the mean arterial pressure to control levels in rats with lesions. Thus, the chronic effects of nucleus tractus solitarii lesions in rats are to abolish the cardiomotor component of the baroreflexes and to produce extreme lability of the arterial pressure without altering the average level of the mean arterial pressure. Exaggerated blood pressure responses are seen in association with various behaviors. These effects are mediated primarily by changes in sympathetic discharge to the vasculature and are independent of the ambient level of environmental stimuli. (Circ Res 54: 227-238, 1984)

THE possibility that altered central nervous system regulation of the arterial blood pressure may participate in the initiation or maintenance of some forms of hypertension has received increased attention in recent years (Brody et al., 1980; Buckley and Ferrario, 1981). Attempts to produce animal models of neurogenic hypertension often have been directed at increasing sympathetic discharge, for example, by direct activation of cardiopressor centers via electrical stimulation (Folkow and Rubinstein, 1966; Bunag and Riley, 1979), or by subjecting animals to stressful behavioral conditioning procedures (Smith, 1974; Buchholz et al., 1981). The elevations in arterial pressure caused by these procedures are modest and not sustained.

Alternatively, some studies have attempted to produce hypertension by removing the tonic inhibition of the baroreceptors on sympathetic nerve activity by either peripheral denervation of the baroreceptors (sinoaortic denervation) or by placement of electrolytic lesions in the nucleus tractus solitarii (NTS) of the caudal medulla, the primary site of termination of baroreceptor afferents (Berger, 1979; Wallach and Loewy, 1980; Davies and Kalia, 1981). Sinoaortic denervation in rats and dogs eliminated the baroreflexes and produced increased lability of the arterial pressure with or without an increase in mean arterial pressure (MAP) (Krieger, 1964; Ferrario et al., 1969; Cowley et al., 1973; Alexander et al., 1980; Ito and Scher, 1981; Norman et al., 1981).

Lesions of the NTS produced a significant increase in the average level and lability of the MAP in cats (Nathan and Reis, 1977) and an elevated MAP in dogs which may or may not be associated with increased lability (Laubie and Schmitt, 1979; Carey et al., 1979). Cowley et al. (1973, 1980) have suggested that the elevated MAP reported in many of the studies resulted from increased responsiveness of debuffered animals to environmental stimuli and the methods used to record cardiovascular responses.
The acute effects of central disruption of the baroreflexes were first studied in the rat by Doba and Reis (1973). Bilateral electrolytic lesions of the NTS abolished the baroreflexes and produced fulminating hypertension due to a sympathetically mediated increase in total peripheral resistance. This was followed by cardiac failure, pulmonary edema, and death within hours. Zandberg et al. (1978) reported that chronic hypertension also developed in the rat following placement of lesions in the NTS. The animals were pretreated with reserpine which, by depleting catecholamine stores, blocked the sympathetically induced rise in total peripheral resistance and mitigated the acute effects of the lesions, thus allowing the rats to survive. This study, while producing a chronic model of NTS hypertension in the rat, had several shortcomings. First, the lesions were large, destroying far more than the region of the NTS. Second, postlesion baroreflex activity was variably affected. Therefore, the hypertension could have been due to more than simply central debudding of the animals. Third, it could not be ascertained whether the form of hypertension was sustained or labile because of the recording techniques used to assess cardiovascular activity.

The present study was designed to assess more adequately the chronic effects of NTS lesions in rats, first, by placement of more discrete lesions in the intermediate portion of the NTS, thereby more consistently eliminating baroreflex function, and second, by chronically recording arterial pressure via indwelling cannulas. The animals were protected against the acute effects of the NTS lesions by reducing sympathetic nerve transmission with periodic administration of sodium pentobarbital (Harvey, 1980). Comparisons of cardiovascular activity recorded under conditions of controlled and uncontrolled environmental stimulation were also made to assess the impact of environmental stimuli on the average level and lability of the MAP in rats with NTS lesions.

**Methods**

**Subjects**

Experiments were performed in male Long-Evans rats (Blue Spruce Farms) weighing 350–550 g. The rats were housed individually in standard laboratory cages, and had ad libitum access to food and water. The experimental group consisted of 18 rats in which electrolytic lesions were placed in the NTS. The controls consisted of unoperated (n = 16) and sham-operated (n = 10) rats. The rats were maintained on a 12-hour light-dark cycle. Data were collected on 55% of the rats 5–8 weeks after placement of NTS lesions. We tested the remaining rats at 1 week and 28 weeks postlesion, in order to determine whether the cardiovascular response changed over time.

**Placement of NTS Lesions**

After premedication with atropine sulfate (0.1 mg/kg, sc), the rats were anesthetized with sodium pentobarbital (50 mg/kg, ip) and placed in a stereotaxic apparatus (Kopf) with the head flexed to an angle of 25–30 degrees. A mixture of 50% oxygen-50% nitrogen or 100% oxygen was blown over the nose through a face mask (2 liters/min). A portion of the occipital plate was removed, and dissection of the dura and arachnoid membranes allowed direct visualization of the dorsal surface of medulla at the level of the area postrema. Bilateral electrolytic lesions were placed in the NTS at the level of the obex, using the following coordinates: anterior 0.3–0.5 mm from the caudal tip of the area postrema, lateral 0.8–0.9 mm from midline, and −0.5 mm below the surface of the brain. Anodal lesions were made by passing a DC current (0.75–1.0 mA) through a Teflon-coated tungsten wire (0.18 mm o.d., 0.2-mm tip exposure) for 5–7 seconds. After completion of the surgery, the brainstem exposed by the craniotomy was covered with Gel-foam soaked in saline, and the neck muscles and skin were approximated with suture. A light plane of anesthesia was maintained for another 8–10 hours with supplemental doses of pentobarbital (16 mg/kg, ip), given hourly or as needed. Atropine was supplemented hourly (0.05 mg/kg, sc) to reduce mucus secretions. Throughout this period, 100% oxygen or the oxygen-nitrogen gas mixture was blown over the noses of the rats. Finally, all rats spent another 8–12 hours in a recovery chamber through which the oxygen-nitrogen gas mixture was passed. Sham-operated rats were exposed to the same procedures as rats receiving lesions, with the exception that after positioning the electrode in the NTS, current was not passed.

**Cardiovascular Instrumentation and Monitoring**

In a second operation, the rats were anesthetized with either halothane (2% in 100% oxygen) blown over the nose through a face mask (2 liters/min) or sodium pentobarbital (50 mg/kg, ip). A cannula filled with heparin in normal saline (50 U/ml) was inserted into the left femoral artery and threaded into the abdominal aorta. The tip of the cannula always lay distal to the branching of the renal arteries. A second cannula filled with heparinized normal saline was inserted into the left femoral vein and passed into the inferior vena cava. The cannulas consisted of a 4-cm length of Teflon tubing (0.38 mm, i.d.) mechanically bonded to a 45 cm length of Tygon tubing (0.5 mm, i.d.). The cannulas were fashioned by temporarily dilating the Tygon tubing after immersion into ethylene dichloride (Fisher) for 4 minutes. The mechanical bond was achieved by inserting 5 mm of the Teflon tubing into one end of the Tygon tubing and then allowing the Tygon to shrink back to its original size. The cannulas were sutured to soft tissue and the free ends passed subcutaneously and exteriorized through an incision at the top of the skull. Each cannula was threaded through a 13-gauge stainless steel tube cut to a length of 1.5 cm. The tubes were positioned vertically to the top of the skull and cemented in place with dental acrylic (Tef-Cast). The venous cannula was flushed, and sealed with a stainless steel plug. The rats then were placed in a 30 cm × 30 cm × 30 cm clear Plexiglas box containing a grid floor and 12-V house light. The arterial cannula, protected by a light-weight metal spring, was attached to a hydraulic swivel (Instech), thereby allowing the rat complete freedom of movement throughout the cage. Patency of the arterial cannula was maintained by infusion of heparinized normal saline (0.17 ml/hr). The venous cannula was flushed once daily with 0.1 ml of heparinized saline. All rats were treated with a single injection of Bicillin...
(60,000 U) and allowed approximately 48 hours recovery before their cardiovascular activity was monitored.

We recorded arterial pressure and heart rate (HR) in the conscious, freely moving rat by connecting the arterial cannula via the fluid swivel to a pressure transducer (Bentley, model 800) placed at heart level outside the box. The rat remained undisturbed during this process. Pulsatile and mean arterial pressures and heart rate, derived by a cardiotachometer (Beckman 9857) triggered by the systolic pressure pulse, were recorded on separate channels of a recorder (Beckman R611). Pulsatile arterial pressure was sampled at 200 Hz by an analog-to-digital converter and processed by a computer (Digital Equipment Corp., PDP 11/34).

Assessment of Environmental Stimuli on Cardiovascular Response Levels

To assess the impact of ambient environmental stimuli on the mean level and lability of arterial pressure, we recorded cardiovascular activity in all rats while they were exposed to conditions of uncontrolled and controlled levels of environmental stimulation. The uncontrolled stimulation condition consisted of placing the Plexiglas box that housed the rat in an open laboratory environment. The controlled condition consisted of placing the Plexiglas box, containing the rat, inside a sound-attenuating chamber. Frequency histograms were generated from the data collected during each recording period. The mean and standard deviation were calculated for each frequency histogram distribution.

The standard deviation served as an index of lability. The SD served as an index of lability. The SD were generated from the data collected during each recording period. The mean and standard deviation were calculated for each frequency histogram distribution.

Baroreceptor Reflex Testing

The cardiac component of the baroreceptor reflexes was assessed by measuring the reflexively mediated lengthening of interbeat interval (IBI) in response to an acute rise in arterial pressure after a bolus injection of phenylephrine (2-4 μg/kg, iv). The portion of the pressor response used for analysis of baroreflex function consisted of the maximum systolic arterial pressure (SAP) point of each cardiac cycle beginning with the first SAP point that exceeded baseline and ending with the peak SAP of the pressor response. The IBIs of the same number of cardiac cycles were selected and began with the first SAP point of the maximum cardiac cycle that exceeded baseline and ended with the peak SAP of the pressor response. The IBIs of the same number of cardiac cycles were selected and ended with the peak SAP of the pressor response. The IBIs of the same number of cardiac cycles were selected and began with the first SAP point of each cardiac cycle that exceeded baseline and ended with the peak SAP of the pressor response. The IBIs of the same number of cardiac cycles were selected and began with the first cardiac cycle in which the IBI exceeded baseline. Baroreflex sensitivity (BRS) was computed as the slope of the change in IBI as a function of increasing SAP. The relationship between SAP and IBI was statistically tested and found to be significantly nonlinear. Thus, the slope was found by determining the curve of best fit through the scatter plot of IBI and SAP using the equation $Y = a + bX + cX^2$. The mean of the first derivative of all points on the BRS curve was used as a measure of the slope (Nathan and Reis, 1980). This second-degree equation more closely fits the scatter plot of IBI and SAP when the relationship between these variables departs significantly from a linear function. The equation can also be used appropriately in cases where there is nonsignificant departure from linearity. In such cases, the $cX^2$ term becomes quite small and the second degree equation closely approaches the first degree equation $Y = a + bX$.

Autonomic Blockade

Sympathetic and parasympathetic influences on the mean level, and lability of arterial pressure and heart rate, were assessed in 8 control rats and eight rats with NTS lesions by means of pharmacological blockade with methyl atropine (1 mg/kg, iv), dl-propranolol HCl (1 mg/kg, iv), and prazosin HCl (1 mg/kg, iv). After one-half hour baseline recording of cardiovascular activity, atropine, propranolol, and prazosin were administered sequentially. A one-half hour recording of cardiovascular activity was made 5-10 minutes after the administration of each drug. Efficacy of blockade for each drug was tested in selected animals immediately before commencement of the recording session by administration of the appropriate agonist, either acetylcholine (2 μg/kg, iv), isoproterenol (1 μg/kg, iv), or phenylephrine (4 μg/kg, iv), respectively. All recordings were made outside the sound-attenuating chamber. Frequency histograms were generated for each variable under each drug condition, and the mean and standard deviation were calculated for each frequency histogram distribution.

Histology

At the conclusion of the experiment, the rats were anesthetized with sodium pentobarbital (50 mg, iv) and killed by intracardiac perfusion with normal saline followed by 10% buffered formalin. The brainstems were removed and stored in buffered formalin. Frozen (40-μm) or paraffin (15-μm) sections were cut serially, mounted, and stained, by the Klüver-Barrera procedure (Klüver-Barrera, 1953). In some cases, alternate paraffin sections were stained with cresyl violet or Weil stain. Microscopic examination of the sections was performed to localize and determine the extent of each lesion.

Statistics

Differences in cardiovascular responses between rats with lesions of the NTS and control rats under conditions of controlled and uncontrolled environmental stimulation or under autonomic blockade were evaluated for statistical significance using a two-factor analysis of variance, with repeated measures on one factor (Winer, 1971). Post hoc analysis of significant effects was performed with a Tukey (a) multiple comparisons test. An unpaired Student’s t-test was used to compare baroreflex sensitivity in rats with NTS lesions and in control rats. A probability level of $P < 0.05$ was taken as statistical significance for all tests.

Results

Effects of NTS Lesions on Arterial Pressure and Heart Rate

The lability of the arterial pressure increased markedly in rats with NTS lesions (Fig. 1). Minute-to-minute variations in MAP of 100–140 mm Hg were common, with fluctuations as large as 170–180 mm Hg occasionally observed. Frequently, these changes were seemingly spontaneous, as they oc-
Control NTS Lesion

![Graph showing arterial pressure and heart rate comparison between control and NTS lesion rats.](image)

**Figure 1.** Effect of NTS lesions on the arterial pressure and heart rate of conscious, freely moving rats. Note the extreme lability of the arterial pressure following placement of NTS lesions in contrast to the relatively stable response levels of the control rat. These rats were selected for display because their average level and lability of MAP and HR are representative of their overall group average.

curred in quiet, awake rats and were unassociated with any particular behavior or identifiable stimulus. In comparison, control rats exhibited relatively stable pressures, with changes in MAP usually not exceeding 20–30 mm Hg. Variations in arterial pressure were not necessarily related to changes in heart rate for either group.

The average MAP, computed from the frequency histograms, was not significantly different between the lesion and control groups, regardless of whether the rats were exposed to conditions of controlled or uncontrolled environmental stimulation (Table 1). The range of the average MAPs in rats with NTS lesions (95–132 mm Hg) was virtually the same as that seen in controls (97–132 mm Hg). In addition, NTS lesions did not significantly affect the average value or variability of the heart rate, although both groups displayed slightly higher heart rates when exposed to an uncontrolled environment. There was no significant correlation between MAP and heart rate for either group.

However, lesions of the NTS resulted in a striking increase in the lability of the MAP (Table 1). The average standard deviation of the MAP in rats with lesions was approximately 380% greater than that of control rats. The significantly greater lability of the MAP in the lesion group is best illustrated by comparing the shapes of their frequency histograms (Fig. 2) with those of the control group (Fig. 3). The frequency histograms of the control group characteristically displayed a prominent peak and narrow range. The lesion group showed a much wider dispersion of MAP, with no dominant peak exhibited. The lability of the arterial pressure in rats with NTS lesions was not influenced by the environmental conditions to which the rats were exposed (Table 1). The enhanced lability was observed in rats as early as 7 days after placement of lesions (the earliest period of postlesion evaluation), and appears to be a permanent effect, since it persisted unaccompanied by an elevation in MAP in three rats observed more than 6 months after placement of NTS lesions. The degree of lability observed at 7 days and 6 months was not different.

**Effects of NTS Lesions on Baroreceptor Reflex Function**

Bilateral lesions of the NTS completely abolished the reflex bradycardia normally observed in response to a phenylephrine-induced increase in ar-

**Table 1**

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<thead>
<tr>
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<th>Controlled stimulation</th>
<th>Uncontrolled stimulation</th>
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<tr>
<td></td>
<td>Control (n = 26)</td>
<td>Lesion (n = 18)</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>114 ± 1.6</td>
<td>112 ± 1.8</td>
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<tr>
<td>sd MAP (mm Hg)</td>
<td>6.4 ± 0.4</td>
<td>23.9 ± 1.8*</td>
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<tr>
<td>HR (beats/min)</td>
<td>350 ± 5.1</td>
<td>364 ± 8.8</td>
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<tr>
<td>sd HR (beats/min)</td>
<td>31.5 ± 2.0</td>
<td>28.3 ± 1.8</td>
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All values expressed as mean ± SEM.

*P < 0.05.
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CONTROL RATS - CONTROLLED STIM (N=5)
MEAN = 114.9 ± 6.19

Figure 3. Frequency histogram distributions of mean arterial pressure from five control rats. Blood pressure was recorded for 1 hour under conditions of controlled stimulation. These rats were selected for display because their mean level and lability of the MAP are representative of their overall group average. The average and standard deviation (x) of the mean arterial pressure are shown in the upper left of the figure.

The slopes of the BRS curves for rats in the lesion group (Fig. 5) were typically close to zero, contrasting sharply with the clearly positive slopes of the BRS curves for the control group (Fig. 6). The relatively high heart rate of the rat (4-9 beats/sec), coupled with an estimated 0.5-1.0 second latency of the cardiac component of the baroreflex (Coleman, 1980; Struyker-Boudier et al., 1982), produced a delay in the start of the reflex-mediated slowing of the heart rate in control animals by one to eight cardiac cycles after the initial rise in systolic arterial pressure. Since rats with NTS lesions did not demonstrate a reflex bradycardia, we utilized the mean cardiac cycle delay of the control group (four cycles) to determine the first cardiac cycle from which to begin the selection of the IBIs used in plotting the BRS curves for these animals. The mean slope of the BRS curves of the lesion group (n = 18, -0.096 ± 0.021 msec/mm Hg) was significantly less than that of the control group (n = 26, 0.813 ± 0.057 msec/mm Hg, P < 0.05). In addition, no correlation was found between baseline heart rate and baroreflex sensitivity in the control rats.

Effects of Autonomic Blockade on Cardiovascular Activity

The effects of muscarinic blockade with atropine or β-receptor blockade with propranolol did not significantly affect the average level or variability of the MAP of lesion or control groups during the one-half hour recording sessions taken under each drug condition (Fig. 7). However, subsequent blockade of α1-receptors with prazosin resulted in a significant reduction in MAP for both groups. The decrease in arterial pressure was significantly greater in rats with NTS lesions (42 ± 6 mm Hg, 38.3%) than in control rats (27 ± 4 mm Hg, 23.2%). Prazosin also produced a reduction in the lability of the MAP in rats with lesions to a level not significantly different from that of control rats. Prazosin had no effect on the lability of the MAP of the control group. Atropine treatment significantly increased heart rate while decreasing heart rate variability in both groups (Fig. 8). Treat-
ANIMAL: UC 7
FILE: UC73.DAT; I
OPTION: 2
MODEL 2: Y=a+bx+cx^2
DELAY: 2
SLOPE: 0.879
R^2: 0.895

SYSTOLIC ARTERIAL PRESSURE (mm Hg)

FIGURE 6. Graph of the scatterplot and line of best fit from the baroreflex test for the control rat in Figure 4. This rat was selected for display because its baroreflex sensitivity was representative of the control group's average baroreflex sensitivity. The slope, R^2, and delay are computed as described in Figure 5. The lengthening of the IBI with the rise in systolic arterial pressure yielded a positive slope in this rat, indicating normal baroreflex function.

ment with propranolol and prazosin resulted in parallel reductions in heart rate, with no further change in heart rate variability for either group.

Effect of NTS Lesions on Cardiovascular Responses during Natural Behaviors

Lesions of the NTS not only increased the range of spontaneous fluctuations of arterial pressure but, also, greatly exaggerated the small changes in arterial pressure normally associated with naturally occurring behaviors, such as eating, drinking, and grooming (Fig. 9). These changes were similar, although larger in magnitude, to those previously observed in cats with chronic NTS lesions (Nathan and Reis, 1977). Increases in MAP to levels that often exceeded 200-220 mm Hg were seen in rats with NTS lesions during eating and drinking behaviors.

Exaggerated increases in MAP were also displayed during grooming, but were usually smaller. Often, the performance of consummatory behaviors by rats with lesions evoked a pronounced dysrhythmia in the heart rate not usually observed during other behaviors (Fig. 9B). Beat-to-beat decreases in heart rate of 120 beats/min were common. The frequency of occurrence of the dysrhythmia was particularly intensified during drinking behaviors. Control rats also exhibited a slight dysrhythmia, with smaller and less frequent changes in heart rate during eating and drinking. The heart rate changes observed during grooming were indistinguishable between lesion and control rats. The mechanism responsible for the dysrhythmia was not investigated, but may be of vagal origin, given its consistent decelerative nature and rapid occurrence.

Localization of Lesions

Lesions that eliminated the cardiac component of the baroreflexes and increased the lability of MAP destroyed all of the solitary tract and variably damaged the medial and lateral NTS at the site of maximal damage (Fig. 10). The lesions also caused minor, but variable, damage to the dorsal motor nucleus of the vagus at various levels rostral and caudal to the obex, as well as minimally damaging the nucleus intercalatus and nucleus gracilis at the most caudal extent of some lesions. The site of maximal damage of the lesions was located at a mean distance of 48 ± 31 µm caudal to the obex. The average rostral-caudal extent of the lesions was 554 ± 23 µm, with an average maximum diameter of 420 ± 38 µm. In five rats, lesions were restricted to the NTS region, leaving all surrounding nuclei.

FIGURE 7. Effects of autonomic blockade with methyl atropine (1 mg/kg, iv), d,l-propranolol HCl (1 mg/kg, iv), and prazosin HCl (1 mg/kg, iv) on the average level (A) and lability (B) of the mean arterial pressure during one-half hour recordings in control (n = 8) and lesion (n = 8) rats. Only α1-receptor blockade with prazosin significantly affected the average level and lability of the mean arterial pressure in rats with NTS lesions. Values represent means ± SEM. Asterisk indicates significant differences, P < 0.05.
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Heart Rate (bpm)

360-

320-

280-

240-

200-

160-

120-

80-

40-

0-

35 -

30 -

25 -

20 -

15 -

10 -

5 -

0 -

SD of Heart Rate (bpm)

FIGURE 8. Effect of autonomic blockade with methyl atropine (1 mg/kg, iv), dl-propranolol HCl (1 mg/kg, iv) and prazosin (1 mg/kg, iv) on the average heart rate (A) and heart rate variability (B) during one-half hour recordings in control (n = 8) and lesion (n = 8) rats. Rats with NTS lesions showed changes in heart rate and heart rate variability that were parallel with those of control rats. Asterisks indicate significant differences, P < 0.05.

Discussion

We have demonstrated that bilateral electrolytic lesions of the NTS in the rat eliminate the cardiomotor component of the baroreflexes and result in extreme lability of the arterial pressure, without altering the average level of the MAP. Moreover, these changes appear to be independent of the level of environmental stimulation to which the rats are exposed. Exaggerated cardiovascular responsiveness to naturally occurring behaviors was also exhibited by rats with NTS lesions. These responses were mediated primarily by fluctuations in sympathetic vasomotor tone. The average level and variability of the heart rate was unaffected by placement of the lesions.

Previous studies have demonstrated that chronic chemical or electrolytic lesions of restricted portions of the NTS can alter baroreflex function and central blood pressure regulation in the rat (Snyder et al., 1978; Talman et al., 1980). Whereas these lesions resulted in a moderate depression of baroreflex sensitivity and modest increase in the lability of the arterial pressure, they principally destroyed only the catecholaminergic innervation of the caudal NTS arising from the A2 neuron group, and left primary baroreceptor afferents intact. In contrast, the lesions placed in the NTS in the present study completely abolished the baroreflexes, and produced a profound increase in the lability of the MAP that was 70–80% greater than that observed in the two earlier studies (Snyder et al., 1978; Talman et al., 1980). The lesions eliminated mainly the tractus solitarii.

intact. No difference was found between the cardiovascular responses for these rats (MAP = 115 ± 2.7 mm Hg, sd of MAP = 24.37 ± 1.76 mm Hg) and those of the entire lesion group. Additionally, lesions in one rat primarily destroyed the lateral NTS and only partially damaged the solitary tract, leaving the medial NTS intact. Baroreflex activity was abolished, but lability was increased only slightly in this animal.

FIGURE 9. Effect of lesions of the nucleus tractus solitarii (NTS) on changes in arterial pressure and heart rate associated with naturally occurring behaviors of a control (A) and a lesion (B) rat. The arrows indicate the onset and offset of a particular behavior. The control rat went directly from eating to drinking as denoted by a single arrow marking the end of the eating and the beginning of the drinking behaviors.
FIGURE 10. Coronal sections of the caudal medulla at the level of the obex in a control rat (upper) and a rat with NTS lesions (lower). The lateral aspect of the lesions are indicated by the arrows. Lesions are at site of maximal damage. Abbreviation: nX = dorsal motor nucleus of the vagus nerve; nXII = nucleus of the hypoglossal nerve; NTS = nucleus tractus solitarii; Ts = tractus solitarii; V4 = fourth ventricle. Weil stain; bar = 1 mm.
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with variable damage to the medial and lateral NTS, and, thus, presumably destroyed primary baroreceptor afferent fibers, while leaving the somewhat more caudal A2 region substantially intact. The more complete disruption of the baroreflexes may account for the more pronounced lability of the MAP observed in our study.

Despite the complete disruption of baroreflex function and the increased magnitude of the arterial pressure variability following NTS lesions, the average level of the mean arterial pressure remained unchanged. Earlier studies showed that the acute effect of destruction of baroreceptor afferents centrally was fulminating hypertension (Doba and Reis, 1973; Dejong and Palkovits, 1976). In the current study, we blocked the acute hypertension, that produces left heart overload, pulmonary edema, and results in death within hours (Doba and Reis, 1973; Dejong and Palkovits, 1976) so that the chronic effects of the lesions could be assessed. However, we also found in preliminary studies that rats with NTS lesions comparable to those described here died when not protected from the acute effects of the hypertension by administration of pentobarbital and the other post-lesion procedures detailed in this report.

The single study that previously evaluated the chronic effects of NTS lesions in rats reported sustained hypertension and tachycardia in reserpine-pretreated rats (Zandberg et al., 1978) and, thus, is at variance with our findings. In contrast to our study, where all cardiovascular measurements were made continuously through chronic indwelling cannulas, these investigators primarily used the tail cuff method to assess the level of the arterial pressure and heart rate, although arterial cannulas were implanted for assessment of baroreflex function as a final procedure. Recordings of arterial pressure made for 30 minutes prior to baroreflex testing showed that the MAP of the lesion group was 167 mm Hg, compared with 122 mm Hg in the control group. The degree to which their rats were undisturbed by intrusions, such as handling, prior to direct recording of arterial pressure was not specified. We observed marked elevations in pressure in lesioned rats after handling that persisted for some time. In addition, it is unclear if the reported group means were based on averages taken over the entire 30-minute recording period or whether the mean was based upon single measurements taken from each rat immediately prior to elicitation of the baroreflexes. If the latter was the case, then relatively high values of arterial pressure could have been selected, particularly if the pressures were as labile as our own findings indicate. Zandberg et al. (1978) did not quantify the variability of the arterial pressure in their animals, although the lack of increase in the heart weight-to-body weight ratio suggests that it was labile. Increased heart weight-to-body weight ratios commonly occur in rats with sustained hypertension (Pfeffer et al., 1973). Finally, we found that lesions that destroyed the solitary tract and damaged only portions of the medial and lateral NTS eliminated the baroreflexes without producing hypertension. The lesions made by Zandberg et al. (1978) were much larger than ours. However, their lesions failed to abolish baroreceptor activity completely in all rats. Therefore, large lesions may destroy additional areas that normally inhibit sympathetic activity, thereby producing sustained hypertension that is, at least in some animals, partially independent of the effect on baroreflex function. In support of this possibility, several studies which reported persistent elevations in MAP after placement of chronic NTS lesions in cats and dogs also made large lesions (Nathan and Reis, 1977; Laubie and Schmitt, 1979; Carey et al., 1979).

Comparison of our results with those obtained in rats after sinoaortic denervation also reveal some similarities and differences. In general, both procedures produce increased lability of MAP. However, the effect of these procedures on the average level of MAP in the rat is a matter of continuing controversy. Whereas neurogenic hypertension has been reported in the rat following peripheral denervation of the carotid sinus and aortic baroreceptors, these studies used measurement techniques that required the rats to be restrained (Krieger, 1964; Alexander, et al., 1976; Chalmers et al., 1979). When continuous measurements were made in unrestrained rats, arterial pressure was labile and only mildly elevated (15-16%) (Jones and Hallback, 1978; Alexander et al., 1980). More recently, Norman et al. (1981) reported that unrestrained sinoaortic denervated rats were normotensive when arterial pressure was measured continuously for 24 hours. The same rats, however, were hypertensive when restrained, regardless of whether pressure measurements were made continuously or with the tail cuff method. Similarly, the results of the present study demonstrate that NTS lesions do not produce hypertension when arterial pressure is measured continuously in unrestrained rats. Hence, an apparently increased reactivity to the stress of restraint may be responsible for the reported increase in arterial pressure in rats deprived of the buffering capacity of normal baroreflex function.

In the cat and dog, differential effects between NTS lesions and sinoaortic denervation on the average level of MAP have also contributed to the controversy (Ferrario et al., 1969, Nathan and Reis, 1977; Laubie and Schmitt, 1979; Carey et al., 1979; Ito and Scher, 1981). Ferrario et al. (1969), recognizing the potential influence of measurement technique and environmental stimuli on elevating cardiovascular response levels, trained chronically instrumented dogs to lie quietly on a pad in the laboratory. Under these conditions, they still observed a 30 mm Hg increase in pressure in sinoaortic denervated dogs. In contrast, Cowley et al. (1973,
1980) found that disruption of the baroreflexes in dogs did not chronically raise arterial pressure when the influence of environmental stimuli was minimized by testing the dogs in quiet rooms. They suggested that the increased MAP observed in many studies is due to the conditions under which cardiovascular responses were recorded. In cats with NTS lesions, we found that the MAP was elevated during the day when the animals were exposed to a busy laboratory environment (Nathan and Reis, 1977). At night, when the laboratory was relatively quiet, the MAP was significantly lower than during the day, although still elevated above control levels. These findings further suggest that the level of the MAP is markedly affected by the impact of environmental stimuli. Therefore, in the present study, we systematically evaluated the influence of the environment on the cardiovascular activity of baroreceptor denervated rats by exposing them to controlled and uncontrolled levels of ambient stimulation. We found that the ambient level of environmental stimulation had no effect on the average level or lability of the MAP in rats with NTS lesions. This confirms the casual observations of Norman et al. (1981), who failed to see any hyperresponsivity in sinoaortic denervated rats to the stimulation provided by an active laboratory environment. The difference in the reactivity of rats and other species to environmental stimulation after NTS lesions may also be due to the more discrete lesions placed in the rat. Possibly, the larger lesions in the cat and dog may have destroyed other central structures or projections that enhanced the ability of environmental stimuli to influence the lability and average level of the MAP. However, this appears unlikely given the fact that in dogs and cats after sinoaortic denervation, a presumably more discrete form of denervation, exaggerated cardiovascular responsiveness was still exhibited to environmental stimuli (Guazzi and Zanchetti, 1965; Ferrario et al., 1969; Cowley et al., 1973, 1980). Thus, unlike the rat, general environmental stimulation may strongly influence the variability and mean pressure in centrally or peripherally baroreceptor denervated cats and dogs. The influence of environmental stimulation on cardiovascular response levels in the dog and cat, however, can only be adequately assessed by testing the same animals in different environmental conditions, such as we did in the present study.

The profound lability of the MAP observed in rats with NTS lesions appeared to be caused by alterations in sympathetic nerve traffic to the vasculature rather than by changes in cardiac sympathetic or parasympathetic activity. This conclusion is supported by several observations. First, atropine and propranolol had no effect upon the average level and variability of the MAP of either the lesion or control rats. Second, only prazosin, a selective α₁-adrenergic blocker, reduced the variability of the MAP in the lesion group to a level comparable to that of the control group. Prazosin also lowered the average level of the MAP of lesion and control rats, but the decrease was significantly greater in the lesion group. Since sympathetic vasoconstrictor tone was blocked in both groups, it is unlikely that baroreflex-induced increases in sympathetic discharge accounted for the lesser fall in pressure in control rats. The differential response to prazosin in NTS lesion and control rats may reflect an elevated total peripheral resistance accompanied by a depressed cardiac output in the lesion rats. The reduction in vasomotor tone by prazosin, combined with an inability to increase an already depressed cardiac output reflexly, could lead to a greater fall in arterial pressure in the lesion rats. Alternatively, other neurohumoral mechanisms, e.g., vasopressin or renin release, which are modulated by the baroreflexes, may have limited the fall in pressure in the control rats (Cowley et al., 1974; Graham and Pettinger, 1979; Thames and Schmid, 1981).

It appears that the NTS lesions performed in the present study had a differential influence on sympathetic control of the heart rate and vascular resistance. Whereas sympathetically mediated changes in vasomotor tone accounted for the increased variability in the arterial pressure in rats with lesions, the resting level of heart rate and changes in heart rate during various behaviors were similar in both lesion and control animals. The level of heart rate also was similarly influenced by muscarinic and β-adrenergic blockade, suggesting that parasympathetic and sympathetic regulation of the heart rate in the two groups was not different. The decrease in heart rate in both groups following prazosin treatment was probably due to a direct negative chronotropic action on the heart, mediated at least in part by α₁-receptors located in or near the sinus node (Williams et al., 1981; Kupfer et al., 1982; Schwartz et al., 1982). However, a centrally mediated reduction in sympathetic nerve discharge to the heart and vasculature after prazosin administration cannot be disregarded (McCall and Humphrey, 1981).

The fact that neural mechanisms regulating the resting levels of arterial pressure and heart rate are unaffected by NTS lesions suggests that areas lying outside the NTS subserve this function. For example, lesions of the rostral ventral lateral medulla produce a significant reduction in resting vasomotor tone resulting in hypotension, while leaving heart rate unaffected (Dampney and Moon, 1980). Additionally, supramedullary areas may be important in controlling heart rate. There is a strong projection from the central nucleus of the amygdala to the dorsal motor nucleus of the vagus and the nucleus ambiguus (Schwaber et al., 1982). All three of these nuclei are importantly involved in controlling the heart rate (Ciriello and Calaresu, 1979; Kapp et al., 1982). On the other hand, the marked increase in the variability of the arterial pressure after NTS lesions...
may be due to the release of areas thought to be involved in the mediation or origin of sympathetic vasomotor discharge from the tonic inhibition of the baroreceptors, e.g. hypothalamus, amygdala, and rostral ventral lateral medulla, (Hilton and Spyer, 1980; Dampney et al., 1981). All of these areas receive direct projections from the NTS (Loewy and Burton, 1978; Ricardo and Koh, 1978; Dampney et al., 1982) and show increased activity during baroreflex activation (Ciriello et al., 1983).

In conclusion, our findings indicate that central disruption of the baroreflexes by NTS lesions results in increased variability of the MAP similar to that seen after peripheral denervation. However, the average level of the MAP and heart rate is normal when measurements are recorded continuously and unobtrusively. Thus, the baroreflexes appear to be important in regulating minute-to-minute changes in arterial pressure, but are not primarily responsible for determining the average level of the arterial blood pressure. Finally, the fluctuations in vasomotor tone appear to be sympathetically mediated in the rat and are independent of the ambient level of environmental stimuli.

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R A Buchholz and M A Nathan

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