Neurogenic Hypertension Produced by Lesions of the Nucleus Tractus Solitarii Alone or With Sinoaortic Denervation in the Dog

CARLOS M. FERRARIO, M.D., KAREN L. BARNES, PH.D., AND STANISLAV BOHONEK, B.SC.

SUMMARY The cardiovascular effects of bilateral lesions of the nucleus tractus solitarii (NTS) were compared with those of subsequent sinoaortic denervation in the same dogs. Destruction of the lateral but not the medial component of the NTS between +0.5 and 3 mm anterior to the obex produces mild hypertension and tachycardia, not always sustained for more than 2 weeks. Rises in pressure were accompanied by increased lability which was not present regularly in all dogs but correlated with the baseline level of arterial pressure. On the other hand, sinoaortic denervation following lateral NTS lesions produced the first demonstration of fulminant hypertension in the dog, which led to death within hours. These data suggest that, while NTS lesions in the dog probably only partially interrupt central baroreceptor pathways, the addition of sinoaortic denervation completely disrupts baroreceptor inputs to the central nervous system, thus releasing central sympathetic outflow completely from baroreceptor inhibition. (Hypertension 3 (suppl II): 11-112-11-118, 1981)

KEY WORDS • arterial pressure • neurogenic hypertension • nucleus tractus solitarii • baroreceptor reflexes • arterial pressure

The primary importance of the central nervous system (CNS) in the disregulation of arterial pressure in hypertensive states has received support from the demonstration that destructive lesions of the nucleus tractus solitarii (NTS) in the rat can produce hypertension severe enough to cause acute cardiac failure and pulmonary edema.1 In other species, however, NTS ablation does not cause fulminant hypertension; there is also disagreement about its long-term effect on mean arterial pressure (MAP).2,3 This study was designed to determine whether bilateral NTS lesions placed in the dog brain would produce neurogenic hypertension for a period of time longer than that reported in most studies.1-8 In addition, we have characterized for the first time in the dog: 1) the blood pressure lability that accompanies the changes in arterial pressure; and 2) the effect of sinoaortic denervation upon the cardiovascular status of conscious dogs with previous lesions of the NTS.

Methods

Eight trained mongrel dogs were used for these studies. Experiments were started 2 to 3 weeks after the dogs were instrumented with a catheter positioned into the lower abdominal aorta via an iliac artery.6

Experimental Protocol

Dogs were brought to the laboratory for daily training and conditioning after they had been certified by a veterinarian to be in good health and fully recovered from all surgical procedures. During recording sessions they were housed in a pen situated in a dimly lit laboratory, shielded from ambient visual or auditory stimuli. Each recording session lasted from a minimum of 90 minutes to 3 hours, during which time the dogs were confined to the pen but were free to change posture, turn about, or rest quietly.

At the completion of a 15–24 day control period the animals were anesthetized with halothane and mechanically respirated. The lower portion of the medulla oblongata was exposed surgically as described before.6,8 A concentric bipolar electrode (each contact exposed 0.5 mm separated by 1.0 mm) was lowered into the NTS at two positions on each side of the brain, and a 2–5 mA DC current was passed between the contacts for 30 seconds to make each of

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the four lesions. The stereotaxic coordinates for NTS lesions were: 1) 1.0 mm anterior to the obex, 3.0 mm lateral to the midline, and 3.5 mm below the brainstem surface; and 2) 3.0 mm anterior to the obex, 3.5 mm lateral, and depth 3.5 mm.

In some animals, measurements of arterial pressure and heart rate were obtained 15 minutes to 1 hour after termination of the anesthesia. In animals not monitored immediately, measurements were resumed 24 hours after operation and continued almost daily for 3 to 8 weeks. In three dogs with a previous NTS lesion, the procedure of sinoaortic denervation was performed 37 to 52 days later as described by Ferrario et al. Beat-by-beat recordings of phasic arterial pressure were stored on an FM analog tape recorder for later processing by a digital computer as described previously.

Baroreflex Sensitivity

In dogs subjected to cervical sinoaortic denervation, the cardiac baroreflex responses to acute increases in arterial pressure were determined two to three times during the control period and again after NTS lesion. The test was performed by measuring the change in the interbeat interval during administration of a bolus dose of 10 μg/kg i.v. phenylephrine (Neo-Synephrine, Winthrop Laboratories, New York, New York). The average slope of the regression line of pulse interval (computed as the time between two consecutive upshots in the pressure waveform during the expiratory phase of respiration only) on systolic blood pressure was used to estimate baroreflex sensitivity.

Histological Examination

At completion of all experiments the brain stem was removed and placed in a mixture of 30% sucrose in 10% formalin for a minimum of 2 weeks. Serial sections of the medulla were cut at 25 to 50 μm intervals and stained with cresyl violet or neutral red and Luxol fast blue as described previously.

Statistical Techniques

The mean and the standard deviation (SD) of the mean values for arterial pressure and heart rate were computed for each recording session and from the grouping of recording sessions at designated time intervals (i.e., control, 1 week after NTS ablation, etc.). The mean of all session SD during a designated time period was computed for each dog to estimate hemodynamic stability during those recording sessions, as suggested by Ito and Scher and Ferrario et al. We will refer to this value as an index of "intra-session variability." Statistical comparison between experimental and control mean values was made with student's t test for either paired or unpaired data.

Results

The baseline MAP of eight conscious dogs averaged 97 ± 6 mm Hg (X ± sp) during a 15- to 21-day control period. Heart rate averaged 89 ± 15 beats/min. These values are in agreement with those reported previously for trained, unanesthetized dogs. The variability of MAP and heart rate during recording sessions was characterized by the average standard deviation. In these experiments the control intra-session variability for the group as a whole averaged 8.4 ± 0.6 (X ± se) mm Hg for MAP and 23 ± 1 beats/min for cardiac rate. The values do not differ significantly from those reported previously.

Bilateral electrolytic lesions of the NTS produced a mild form of lasting hypertension in five of eight dogs. In the three others, blood pressure and heart rate rose transiently during the first day after operation, returning to control values between the second and fourth days. There were no further changes in the recorded variables during an additional 26 days of daily recording.

In all five animals with hypertension, elevation of MAP was observed during the first 15 days after operation (fig. 1), and hypertension was accompanied by tachycardia in all but one dog (Dog 123-P). After this time heart rate remained elevated (fig. 2) but blood pressure tended to return toward baseline values. Hypertension was initially accompanied by an increase in the lability of MAP as indicated by the larger values of the intra-session standard deviation (fig. 1). The lability was accounted for by increased minute-to-minute fluctuations in arterial pressure as well as exaggerated responsivity to various spontaneous behaviors (sitting, standing, grooming, etc.) (fig. 3). Three weeks after operation, blood pressure lability was present in all recording sessions in only one of the five NTS-lesioned dogs (Dog 467-P, fig. 1); in the other dogs, blood pressure lability was present in some but not all recording sessions. This was reflected in the lack of a statistically significant increase in the weekly averages (fig. 1). The magnitude of the standard deviation (intra-session variability) correlated with the level of MAP for the group of five dogs as a whole (R = 0.65, p < 0.05). Figure 2 shows that, after NTS lesion, intra-session variability for heart rate was decreased in all but one dog (Dog 123-P) during the first 7 days after operation. Thereafter, it remained below control values in all dogs, even though it increased transiently during the second week in two (Dogs 123-P, 467-P, fig. 2) of the five dogs. There was no correlation between the intra-session variability of heart rate and the absolute level of heart rate (R = 0.03, p > 0.05).

At 5 to 8 weeks after NTS lesion, three dogs (Dogs 123-P, 467-P, 516-P) were anesthetized again, and sinoaortic denervation was performed as described in Methods. Sinoaortic denervation in these dogs caused fulminant arterial hypertension (group average 192 ± 14 mm Hg, p < 0.05), which developed within 15 minutes of the termination of halothane anesthesia and was accompanied by marked tachycardia (202 ±
FIGURE 1. Time course of the changes in mean arterial pressure (top) and lability (bottom) (measured by the standard deviation) in five conscious dogs for from 3 weeks (Dog 123-P) to 8 (Dog 729-P) weeks after bilateral lesion of the NTS. Bars are means ±1 se for control (shaded) and experimental periods (clear bars). For Dog 729-P the standard error is not shown between Weeks 6 and 8 because only one recording session was obtained for each of these three weeks. *p < 0.05

FIGURE 2. Time course of the changes in heart rate (top) and variability (bottom) in five dogs before (C) and after bilateral lesion of the NTS.
CENTRAL DEAFFERENTATION AND SINOAORTIC DENERVATION/Ferraro et al.

Figure 3. Distribution curves for mean arterial pressure (left panels) and heart rate (right panels) for each recording session before (A) and during the third week following lesion of the NTS in one dog. Both hypertension and tachycardia are documented by the shift of the daily histograms to the right of the control tracings (A). Increased arterial pressure lability is demonstrated by the change in the shape of histograms after lesion.

14 beats/min, p < 0.05). The elevation of MAP after sinoaortic denervation was essentially of the same magnitude as that recorded within 30 minutes of the previously performed NTS lesion (fig. 4 left). On the other hand, tachycardia (fig. 4 right) after sinoaortic denervation was more pronounced when compared to that recorded within 30 minutes of the NTS ablation (125 ± 33 before vs 202 ± 14 beats/min after sinoaortic denervation, p < 0.05). Death due to acute cardiac failure occurred within 4 to 6 hours after completion of the surgical procedure.

Table 1 shows the effect of NTS lesion upon baroreceptor reflex responsiveness in the three dogs subjected to sinoaortic denervation. In all three animals the averaged slope of the regression line of pulse interval on systolic blood pressure 48 to 72 hours before sinoaortic denervation decreased by 40.4% of control values. This difference was statistically significant (p < 0.05).

Histological analysis revealed that the outcome with respect to changes in arterial pressure and heart rate was related to both the position and size of the lesion within the NTS and surrounding brain stem. In the dogs in which the operation failed to produce any hypertension or lability, the lesion destroyed the solitary tracts and a portion of the adjacent medial

Table 1. Changes in Baroreceptor Sensitivity after Lesion to the Nucleus Tractus Solitarii (NTS)

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Before NTS lesion</th>
<th>After NTS lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope (msec/mm Hg)</td>
<td>r²</td>
</tr>
<tr>
<td>123-P</td>
<td>10.78 ± 3.30</td>
<td>0.85</td>
</tr>
<tr>
<td>467-P</td>
<td>8.10 ± 1.31</td>
<td>1.00</td>
</tr>
<tr>
<td>516-P</td>
<td>5.17 ± 1.04</td>
<td>1.00</td>
</tr>
<tr>
<td>Average</td>
<td>8.02 ± 1.62</td>
<td>-3.24 ± 0.18</td>
</tr>
<tr>
<td>Difference</td>
<td>-3.24 ± 0.18</td>
<td></td>
</tr>
<tr>
<td>Significance</td>
<td>p &lt; 0.005</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± 1 SE of the average slope of the linear regression of pulse interval on systolic pressure, r² is the coefficient of determination. Data were obtained before NTS lesion and between 48 and 72 hours preceding sinoaortic denervation, after NTS lesion.
FIGURE 4. Effect of sinoaortic denervation (SAD) on the mean arterial pressure [left] and heart rate [right] of three dogs (123-P, 467-P and 516-P, fig. 1). The procedure was performed between 28 and 42 days after previous nucleus tractus solitarii (NTS) lesion. From left to right, bars are mean ± 1 se of baseline values before (control), within 30 minutes to 1 hour after NTS lesion and recovery from anesthesia (NTS lesion), the grouped values averaged during the weeks that followed the brain surgery (chronic phase) and finally within 1 hour after SAD. Asterisk denotes statistical significance (p < 0.05) as evaluated by the Student’s t test for unpaired values.

NTS (only between the obex and 1 mm anterior). In contrast, the lesion in the five animals that became hypertensive extended bilaterally from +0.5 to at least 3.0 mm anterior to the obex (fig. 5). For example, the dog with the greatest degree of hypertension (Dog 516-P, fig. 1) had bilateral destruction of the lateral portions of the NTS between +0.5 and 4.0 mm anterior to the obex; however, the solitary tracts were interrupted bilaterally only between +1.0 and 2.0 mm anterior. Another dog (Dog 467-P, fig. 1) with the next greatest cardiovascular effect also sustained bilateral destruction of the lateral NTS from +0.5 to 3.5 mm anterior to the obex, with interruption of only the left solitary tract between +1.5 and 3.0 mm anterior to the obex. The remaining three dogs with less striking cardiovascular effects were found to have considerably less extensive NTS lesions between the obex and 3.0 mm anterior; indeed, in two of these three dogs (Dogs 123-P and 729-P) the solitary tracts were entirely intact.

Discussion

These experiments demonstrate that destructive lesions of the lateral NTS between +0.5 to 3.0 mm anterior to the obex can, in dogs, result in mild hypertension, tachycardia, and variably increased blood pressure lability. In some but not all dogs, MAP was elevated for several weeks after the brain procedure. This observation suggests that a lesion that interrupts most of the central pathway for the baroreceptors in the NTS may lead to a form of neurogenic hypertension lasting for months instead of weeks. On the other hand, fulminant hypertension, as originally described in rats by Doba and Reis, does not occur in the dog; the larger brain stem in this species possibly reduces the chance of trauma to the brain stem. This is of critical importance, considering that at this level of the medulla oblongata there are a number of important nuclei that are involved in the central control of cardiovascular, chemoreceptor, and respiratory functions. Alternatively, rats’ hearts may be less able to cope with a sudden, large increase in afterload. However, dogs did not tolerate complete interruption of baroreceptor reflexes after NTS lesion was combined with peripheral sinoaortic denervation. If the absolute level of arterial pressure is a primary factor triggering the onset of cardiac failure and pulmonary edema, the dogs would not have survived the initial phase of hypertension after NTS lesion and discontinuation of anesthesia. Within 1 hour after NTS lesion, the MAP was found to be as high as that recorded after peripheral sinoaortic denervation several weeks later. On the other hand tachycardia was more pronounced after the second operation. This may compromise cardiac output sufficiently to reduce cardiac reserve to abnormal levels. However, Ferrario and colleagues showed previously that pronounced tachycardia in the dog is a characteristic feature of sinoaortic denervation, with all dogs surviving the procedure.

Therefore, we believe that incomplete central baroreceptor deafferentation allowed as yet uniden-
tified compensatory mechanisms to assist in gradually lowering the arterial pressure. In accord with this idea, we have observed that electrolytic lesions that almost completely destroy dorsal portions of the dog's brain stem, and presumably all baroreceptor input, produce hypertension that terminates in death. The downward shift in the average slope of the regression lines between pulse interval and systolic blood pressure in NTS-lesioned dogs before sinoaortic denervation indicates significant but not complete impairment of the cardiac component of the baroreceptor reflex.

Previous studies regarding production of sustained hypertension by lesions in the NTS of the dog are not conclusive. Carey et al. showed that NTS lesion in the American foxhound was accompanied by mild hypertension. Because measurements were not continued beyond 10 days, it is not known whether the hypertension would have persisted during a longer time span. On the other hand, Laubie and Schmitt reported severe, permanent hypertension in dogs several months after NTS lesion. They also observed that the hypertension after NTS lesion was comparable in magnitude to that observed by them in other dogs subjected to sinoaortic denervation. This is surprising because a number of studies indicate that sinoaortic denervation does not result in either a marked or sustained elevation in arterial pressure unless measurements are obtained in an environment that predisposes the dog to be in an alert state. We avoided this problem by prolonging the recording sessions to several hours instead of minutes each day and keeping the conscious dogs isolated from environmental disturbances.

There are no previous studies of blood pressure lability in NTS-lesioned dogs. The present findings indicate that lability is present in dogs after NTS ablation. However, it is not found consistently in all lesioned dogs beyond the second week after the operation. Failure of persistent lability may be due to incomplete removal of baroreceptor afferents since increased variability is a characteristic feature of sinoaortic denervated dogs. When blood pressure lability was present it had the same features as that previously described in dogs with sinoaortic denervation. Nathan and Reis have shown that in NTS-lesioned cats the magnitude of the blood pressure lability paralleled the degree of hypertension. On the other hand, Reis et al. showed that in the rat increased blood pressure variability can occur independently of any hypertension. The same phenomenon is true in sinoaortic-denervated animals. The present data in the dog suggest that the degree of blood pressure lability correlates with the level of arterial pressure. The same is not true for heart rate.

While lesions of the lateral NTS did not produce an increase in MAP sustained for the duration of the study, additional removal of the four major baroreceptor nerves in the dog's neck several weeks after the NTS lesion caused a drastic change in the cardiovascular system that led to death within hours. Because we compared in the same animals the effects of NTS lesion with those of sinoaortic denervation, it was possible to determine not only similarities but also differences. The acute increase in arterial pressure after either procedure was of comparable magnitude. On the other hand tachycardia was most marked after sinoaortic denervation. Others have noted that NTS lesions do not produce tachycardia during the acute phase of hypertension. It is probable that the large elevations of heart rate after sinoaortic denervation are related to total disinhibition of sympathetic activity as a result of complete interruption of baroreceptor reflexes.

In the present experiments, the NTS lesion, at least as judged by the baroreceptor test, was not large enough to destroy most of the first synaptic relay of the fibers within the brain stem that project from the sinus and aortic baroreceptors. Recent neuro-anatomical studies of the brain-stem projections of baroreceptor afferent fibers in the carotid sinus and aortic depressor nerves by Kalia and Panneton and Loewy have shown that not all of these baroreceptor fibers terminate within the NTS. Both buffer nerves send afferents to the dorsolateral area postrema, while the carotid sinus nerve also appears to contribute fibers to the region surrounding the nucleus ambiguus in the ventrolateral medulla. Chernicky et al. have now shown that in the dog vagal afferents enter the brain stem more than 6 mm anterior to the obex and begin to distribute fibers in the medial NTS anterior to the rostral end of the lesions verified in the present experiments. There is thus the possibility that a significant proportion of vagal afferents entering the medial NTS and the area postrema may exit the solitary tract anterior to the area encompassed by the electrolytic lesion.

In summary, bilateral electrolytic lesions of the NTS produce mild hypertension, not necessarily sustained, most likely due to partial interruption of central baroreceptor pathways. Blood pressure lability is variable and is accompanied by moderate tachycardia and reduced heart rate variability. Sinoaortic denervation performed after NTS lesion produces fulminant hypertension. This suggests that complete disinhibition of sympathetic activity can occur after removal of all of the baroreceptor reflexes. Therefore, complete disconnection of all baroreceptor inputs to the CNS vasomotor apparatus is required to produce a model of sustained hypertension of neurogenic origin. When this condition is met, the ability of the CNS to induce a lethal rise in arterial pressure is fully demonstrated. Partial, rather than total, destruction of baroreceptor inputs at the level of the NTS may thus account for the contradictory results obtained by previous researchers evaluating whether sustained hypertension can be produced by central baroreceptor deafferentation.

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