Naturally occurring hypertension in New World nonhuman primates: potential role of the periformal hypothalamus

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Smith OA, Astley CA. Naturally occurring hypertension in New World nonhuman primates: potential role of the periformal hypothalamus. Am J Physiol Regul Integr Comp Physiol 292: R937–R945, 2007. First published October 5, 2006; doi:10.1152/ajpregu.00400.2006.—Hypertension is a prominent underlying factor in the genesis of cardiovascular-related morbidity and mortality. A major impediment to the investigation into the causes of the disease is the paucity of naturally occurring animal models of the disease. There is evidence that some species of New World primates spontaneously become hypertensive. We used chronically implanted pressure transducers to assess normally occurring blood pressure and heart rate levels at rest and during routine laboratory procedures in a group of one of these New World primates (Aotus sp.). Resting mean arterial pressure ranged from 72 to 130 mmHg. Three animals were judged to have resting mean arterial pressure levels in the hypertensive range (≥110 mmHg). In all of the animals, pressor responses to routine laboratory events were exaggerated (average highest mean pressure during 1 min from any session was 97–196 mmHg). Subsequently, the region of the periformal/lateral hypothalamus known to produce elevated blood pressure and heart rate responses to electrical stimulation was removed, and the blood pressure responses to the laboratory routines were significantly decreased and, in some cases, eliminated. Control lesions in nearby tissue had no effect on these responses. This region may play a critical role in initiating or exacerbating cardiovascular responses that contribute to the development of essential hypertension.

The levels were excessively high. The results of the study of the woolly monkeys in zoos and in private hands have been reported elsewhere (7). The survey of the owl monkeys took place at the Battelle Pacific Northwest National Laboratory (Richland, WA) at the request of Drs. Weller and Baer (1), who were concerned about the incidence of cardiomegaly and associated mortality in the colony of owl monkeys that was maintained at that facility.

The results of direct arterial puncture measurements on 54 monkeys under ketamine anesthesia were striking for their extremely high levels of blood pressure compared with similar measurements in baboons and Macaca nemestrina. Because the immediate effects of capture of the animals and subsequent injection with ketamine on blood pressure are unknown, this series was followed by a pilot project in which blood pressure devices were chronically implanted in the aorta in two monkeys. Pressures were then recorded for several days while the animals were fully awake. Characteristically, systolic blood pressures were 120–150 mmHg during quiet rest but would increase to 220–250 mmHg when the animals were disturbed simply by a technician walking into the area. These increases were also inordinately protracted.

In addition to the cardiac-associated mortality rate found earlier at the Battelle colony, the University of South Alabama reports similar problems in their colony of ~300 owl monkeys and is actively attempting to determine the conditions leading to the elevated incidence of cardiomyopathy and cardiomegaly (C. Abee, personal communication).

These two species of New World primates provide potential models for the study of naturally occurring hypertension. Unfortunately, because the woolly monkey is endangered in the wild and is exceptionally difficult to breed in captivity, it is ethically unacceptable to carry out extensive invasive and terminal experiments. On the other hand, the owl monkey is found in significant numbers in many parts of the Amazon basin. It is being bred at the Proyecto Peruano de Primatologia (Iquitos, Peru) and is actively used in studies of malaria and the visual system and in oncogenic virus research (1).

To continue these studies, we imported a small group of owl monkeys from the breeding colony in Peru under the auspices of the National Institutes of Health (NIH). The animals were used for normative measurements and determination of the mechanism by which the periformal/lateral hypothalamus area might be involved in controlling blood pressure responses, as it is in the higher Old World primates (20–23).

The specific objectives of this research were to determine (1) whether mean arterial blood pressure (MAP) is in the hyper-
tensive range in some members of a group of unanesthetized and freely moving Aotus and 2) whether lesions of the perifornical/lateral hypothalamic area of the hypothalamus, referred to as the defense area or the hypothalamic area controlling emotional responses (HACER), would result in the reduction of the expected hyperreactive blood pressure levels in response to a precisely controlled laboratory procedure and other routine laboratory events.

METHODS

Animals

Twelve young, adult Aotus nancymai were obtained for the project: 10 were imported from Peru via the cooperative program between the NIH and the Peruvian Primatology Project, and 2 were obtained from Georgetown University. One animal was used for measurement of preliminary data and one died, leaving 10 animals: 5 females (animals AG23, AG24, AG53, AG54, and AG64) and 5 males (animals AG11, AG31, AG32, AG41, and AG42) as the study group. The Peruvian animals were held in initial foreign-born quarantine for 30 days at the University of Miami, and all animals subsequently were quarantined at the University of Washington for another 31 days. During this time, special care procedures were instituted, including a high fresh fruit-and-vegetable diet, special caging, protection from unnecessary environmental stimuli, and special training for the animal care personnel. Housing and care of the animals met NIH standards as stated in the “Guide for the Care and Use of Laboratory Animals” (National Research Council, 1996, 7th ed.), Institute for Laboratory Animal Research recommendations, and the American Association for the Accreditation of Laboratory Animal Care standards. The University of Washington, including the Primate Center, is fully accredited by American Association for the Accreditation of Laboratory Animal Care. The Institutional Animal Care and Use Committee approved all procedures.

Apparatus

Cages. The animals were housed in different-sex pairs in large (27 × 34 × 34 in.) cages that included a small standard commercial Styrofoam ice chest, which served as a nest box. A 4 × 4-in. door was cut in the front of the ice chest, drainage holes were cut in the bottom, and the chest was held in place by a metal angle-iron frame. The receiver of the telemetry system was located on top of the frame, immediately above the ice chest. At any one time, recordings were simultaneously made from two animals in different cages.

Telemetry. The pressure measurement-and-telemetry system (Data Sciences International) included completely implantable blood pressure transducer-transmitter components (model TA11PA-C40), general-purpose miniature receivers (model RLA 3000), calibrated pressure-sensor analog adapters (model R11CPA), and ambient pressure reference (model APR-1).

Recording. The details of the recording system have been described by Spelman et al. (25), but only a portion of their system was utilized in this project. The blood pressure pulses from the telemetry system were recorded directly online on a strip-chart recorder (model WR 3010, Western Graphitec) and simultaneously provided to a computer, which determined instantaneous heart rate (HR) from the rising phase of the arterial pressure pulse and computed mean arterial pressure (MAP). These variables were recorded in 1-s bins, stored on the hard drive, and retrieved and processed by a special computer program.

Procedures

Daily routines. At 9 AM, the animal technician entered the room and immediately put a metal divider into the cage, which, in effect, limited the distance the animal could move from the receivers, which had a receiving range of ~18 in. By 10:30 AM, all routine feeding and cleaning procedures were finished and the room was secured. The technicians did not enter the room again until late afternoon, when they fed the animals their second meal and removed the dividers.

Transducer implantation. Animals were sedated with ketamine hydrochloride (Vetalar, 10 mg/kg), and a tracheal tube was inserted. Isoflurane (1.4–1.6%) was utilized for anesthesia. An abdominal incision was made, and the terminal aorta was exposed. The transducer catheter was inserted into the aorta through a small incision made with a 23-gauge needle and fixed to the aorta with a drop of surgical glue. The transmitter-battery unit was attached to the posterior abdominal wall. Tissues were reapproximated, the animals were taken to a recovery area and given butorphenol tartrate (Stadil, 15 mg/kg) for postoperative analgesia. After ~5 days, the baseline CV measurements began.

Prelesion recording. The experimental protocol was simple, precise, and carried out by the same person in every instance for every animal. Early on each recording day, the system was calibrated for ambient atmospheric shifts, and then ~2 h elapsed before data were taken. After a smooth, low-level baseline recording was obtained, the investigators opened the door to the housing area, walked to the cages, and immediately put a metal divider into the cage, which, in effect, limited the distance the animal could move from the receivers, which had a receiving range of ~18 in. By 10:30 AM, all routine feeding and cleaning procedures were finished and the room was secured. The technicians did not enter the room again until late afternoon, when they fed the animals their second meal and removed the dividers.

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Neural procedures. After 1 wk of prelesion recording, the neural procedure was carried out. The animals were sedated with ketamine hydrochloride (10 mg/kg), intubated, anesthetized with isoflurane (1–2%), and then mounted in a Kopf stereotaxic instrument. An intraventricular catheter for lactated Ringer drip was inserted, ECG electrodes were attached, a rectal temperature-measuring device was inserted, a respiratory monitor was activated, and heating pads were placed under and over the animal. A craniotomy was performed under sterile conditions, and a rigid cannula was introduced into a lateral ventricle. For ventriculography, a lateral X-ray was taken immediately after injection of 0.15 ml of metrizamide (radiopaque fluid, Amipaque) into the ventricle, and a frontal X-ray was taken after injection of an additional 0.03 ml of metrizamide. On occasion, somewhat larger volumes of the radiopaque fluid were utilized without detriment. From these images, the precise location of the target structure was obtained, and stereotaxic coordinates for that structure were computed. In accordance with those coordinates, an 18-gauge stainless-steel guide tube was introduced into the brain and stopped above the target structure. A 0.5-mm-diameter insulated electrode with the terminal 1 mm exposed was introduced through the guide tube into the perifornical area. Electrical stimulation (0.5 mA, 100 Hz, 0.1-ms pulse width for 5 s) through this electrode was started ~1 mm below the end of the guide tube. Stimulation was repeated at 0.5-mm intervals until the location producing the maximum CV response to this stimulation was determined. Lesions were then produced by the passage of direct current (2–5 mA for 5–8 s) until the CV responses to a repeat of the stimulation could no longer be elicited. This procedure was carried out bilaterally.

There were a total of 7 animals in the HACER-lesioned group. For the first three animals, the 5-mA current was used; for the other four animals, the 2-mA current was used. In the three control animals, one 2-mA or two 1-mA electrolytic lesions was placed bilaterally in or in the vicinity of the paraventricular nucleus of the hypothalamus. The
animals were given butorphenol tartrate (15 mg/kg) as postoperative analgesic and transported to a recovery area.

The anatomic sites chosen for the lesions were based on previous studies of neural control of the CV system carried out on baboons (20–23). In these earlier studies, we also learned that if the lesion site was misplaced by even <1 mm, the reduction in the magnitude of the CV effect would not occur. This required level of accuracy made the baboon research very difficult, but, in the small owl monkey brain, even greater accuracy was required. Considering this increased probability of missing the correct location, we assigned 7 of the 10 animals to the experimental (HACER) group, believing that some lesions would be asymmetrical or would otherwise miss the proper location and could therefore be used as members of the control group. However, the accuracy provided by the ventriculography in experienced hands determined the stereotaxic coordinates for the locations of the critical lesions and left unbalanced groups of seven and three animals.

Postlesion recording and necropsy. After 1 wk of postlesion recovery, the recording of the CV responses and behavior was resumed. Precisely the same “entering-the-room-and-cage-door-opening” procedures were repeated for 4–6 days. The same random recording of other events that was done preoperatively was done as well. At the end of the experiment, the animals were given lethal doses of pentobarbital sodium. The brains were fixed in situ via intracardiac perfusion with normal saline followed by 10% normal buffered formalin. The brains were removed and, after a several weeks of fixation in formalin, cut into 40-μm frozen sections and prepared with a Nissl stain.

Data editing. Every session recorded was intensively edited for artifacts in the HR or MAP records. The spike artifacts, usually caused by movement, were easily distinguished on the paper chart records and were removed from the computerized records.

RESULTS

Although only a total of 10 Aotus were included in this study, resting MAP was ≥110 mmHg in 3 of the animals (Fig. 1). In the whole group, resting MAP, which was obtained...
After the last disturbance in the room and after the baseline had reached its lowest, constant, nonvarying value just before the “door-open” procedure, ranged from 72 to 130 mmHg [97.5 mmHg (SD 17.02)]. In contrast, during periods of excitement (cage-door-opening procedure or a noncontrolled disturbance such as feeding or cleaning), the average of the highest MAP recorded during 1 min from any of the sessions ranged from 125 to 196 mmHg [157.8 mmHg (SD 23.4)]. This measure was designated the maximal environmentally induced CV response. HR during rest varied from 127 to 178 beats/min [153.7 beats/min (SD 14.5)], and maximal HR varied from 280 to 396 beats/min [350.8 beats/min (SD 37.05)] across the 10 animals (Fig. 1). There were no significant differences in resting or maximal MAP or HR between males and females.

A comparison of the response of the three animals with MAP ≥110 mmHg (arbitrarily designated the hypertensive group) with the three animals at the low end of the distribution (normotensive group) produced comparable shapes in the curves of their response to the “door-open” procedure, with an offset of ~40 mmHg at rest (Fig. 2). In addition, the net increase from the 30th second of the trial (second 30 to second 78) was significantly greater in the hypertensive group. The SPSS one-sample t-test was used to test the null hypothesis that there would be no difference in the amount of increase from rest to maximum between the groups. Even with the small n of 3, the null hypothesis was rejected at P < 0.001. The mean difference was 17.67 mmHg, with an SD of 0.58 and an SE of 0.33. The hypertensive group increased its maximal response by an average of ~18 mmHg beyond the increase demonstrated by the normotensive group; i.e., they not only maintained their initial elevated level difference of 40 mmHg, but they increased that difference by 18 mmHg in response to the procedure. The slopes of the curves after the second inflection point, which occurred at second 36, to the maximal value (second 79) were 0.496 and 0.927 mmHg/s for the normotensive and hypertensive animals, respectively.

The effect of the perifornical (HACER) lesions on the magnitude of the MAP response to the well-defined situation of cage door opening (Fig. 3, top) was to decrease the amplitude of the response. The nonparametric Wilcoxon signed ranks test for two related samples (SPSS program) was used to assess the reliability of the pre- vs. postlesion data. The curves diverge significantly (P < 0.05) at second 47 and continue to be increasingly different between P = 0.046 and P = 0.018 for the remainder of the trial. The HR changes were not as striking as the MAP decreases but, in general, paralleled the changes in MAP, except there was also a significant increase in resting HR after the HACER lesion. The control-lesioned group showed no significant changes in MAP (Fig. 3, bottom) or HR.

Analysis of individual responses provided additional information about the dynamics of this neural area in CV control. Figure 4 illustrates the major elimination of the blood pressure and HR responses to the cage door-opening procedure. Although other animals showed smaller decreases in blood pressure and HR, one animal showed almost complete elimination of the blood pressure response but retained a robust response in HR (Fig. 5).

To obtain a more general picture of the influence of the lesions, we took the average of the highest 60 MAP measurements during each of the recorded sessions and compared them before and after lesion (Fig. 6). Table 1 presents the one-
sample t-test (SPSS) results that tested the null hypothesis that the decreases in these highest responses after lesion were not different from zero. This hypothesis was rejected at $P = 0.004$ for the HACER-lesioned group and failed at $P = 0.982$ for the control group. These measurements were not necessarily sequential; they were simply the average of the highest 60, 1-s, data points during each of the recording sessions. These included the instances of, e.g., cage door opening, room cleaning, and feeding; i.e., each of the 7 or 3 data points used in the statistical analysis was the average of 13–25 measurements before and after lesion, each of which consisted of the 60 highest MAPs during each of the recording sessions that included a disturbance. The very intensive editing procedure provided the validity check that was needed to ensure that none of these peaks were spike artifacts. Concern about the possibility that there might have been a difference in the number and/or quality of the “random events” between the two groups is alleviated by the fact that the animals were run in pairs and each control animal had a cohort HACER-lesioned animal; e.g., animals AG31 and AG32 were recorded at the same time, and, therefore, each animal experienced the identical set of random events, as well as the door-open controlled procedure. This was the same for animal pairs AG41-AG42 and AG53-AG54. Figure 6, which presents the results graphically, illustrates the uniform decrease in the highest MAPs in the HACER group vs. the control group. A parallel measurement was made of the 60 lowest blood pressures produced during those same sessions. This analysis showed no systematic change in the HACER-lesioned animals but demonstrated numerical increases in all of the control animals.

Histograms of the total data sets before and after lesion were prepared for all animals. In four of the seven HACER-lesioned animals, distinct bimodal prelesion distributions of the MAP were replaced after lesion by classic unimodal normal distribution patterns (Fig. 7). Two of the other three HACER-lesioned animals were those (AG64 and AG41) with the lowest maximal responses of the group (Fig. 1), and their distributions showed no bimodality. Among the control-lesioned animals, a bimodal distribution appeared after the control lesion in animal AG32; in another, bimodal distribution was not changed after the lesion; and in animal AG54, the single modal point increased from 116 to 137 mmHg.

The histograms of the HR data illustrate the same fundamental point, but the distributions tended to be characterized by severe skewing (Fig. 7), rather than actual bimodal distribution shapes.

The behavioral responses of the animals to door opening were not systematically recorded. In general, the animals attempted to avoid door opening by running to the opposite end of the cage or hiding in the nest box. The same behaviors...
occurred after lesion, except for one animal that allowed the investigator to touch him. Although actual weighing of the animals would have required interruption of the protocol, the general health and eating behavior of the animals were closely observed and recorded by the animal care personnel on a daily basis. As expected, for 1 or 2 days after a surgical procedure, eating was affected but returned to normal well before the next procedure began.

Because of the limited battery life of the chronic implants, the total duration of these experiments was relatively short; however, the available information indicated that the prelesion levels were stable, showing no major trends in either direction, and that the effect of HACER lesion in reducing the high MAP was maintained over the recorded postlesion period (Fig. 6). The short battery life also precluded carrying out long-term or overnight recording.

The neuroanatomic analysis of the lesion sites reveals that all the HACER lesions were in the vicinity of the targeted perifornical/lateral hypothalamic area (Fig. 8). The control lesions were scattered and asymmetric, except in animal AG42, in which the lesions were precisely in the nucleus paraventricularis of the hypothalamus at this level and at another set of lesions anteriorally as well. Because of the difference in n of the two groups, exact comparability of lesion sizes was not possible. The requirement that current passage be repeated until electrical stimulation did not increase blood pressure also created some discrepancy in lesion sizes. However, there was no difference in the magnitude of the effect of the 5-compared with the 2-mA lesion in response to the door-open procedure. This finding further verifies the earlier work (23) showing the highly localized specificity of the critical neurons in the perifornical region that control these CV responses. The control lesion in animal AG42 more closely approximated the larger HACER lesion, because lesions were made at two different, but proximate, anterior-posterior bilateral sites that merged, amounting to major damage to the paraventricular nucleus. The others received the 2-mA lesions in one bilateral site location.

**DISCUSSION**

The studies were unique, in that they were carried out in primates under freely mobile, untethered circumstances and involved no transcutaneous devices or backpacks. The animals were not behaviorally controlled, and the stimuli used to elicit responses were normal laboratory situations.

Of the 10 animals, 1 had a resting baseline MAP of 130 mmHg with its maximum exceeding 190 mmHg. By human standards, this animal would be considered clinically hypertensive. In two others, resting levels were ~110 mmHg, with maximum levels at ~180 mmHg, an accepted “borderline-hypertension” designation. Because high levels of MAP were produced every time an external disturbance occurred in the laboratory environment, these animals were candidates for the development of pathological levels of blood pressure. These findings provide a physiological basis for the clinical picture of elevated CV-related morbidity/mortality in the breeding colonies of this species, and they are consistent with the preliminary survey in the acute situation where blood pressure was measured under ketamine sedation.

A possible predisposing factor in the production of this hypertension is suggested from the data in Fig. 1, where blood pressure rose to a greater degree in the animals with the highest resting MAP than in any of those with lower resting MAP. As shown in Fig. 2, not only is the increase maintained compared with the normotensive animals, it actually exceeds the expected increases by an average of 18 mmHg. Also, all of these animals with the high resting MAP showed the prominent bimodality in the histograms of the total data set. These data

Table 1. Summary statistics on average changes in highest MAP responses from each of the sessions recorded pre- and postoperatively

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean (SD)</th>
<th>t</th>
<th>df</th>
<th>P (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HACER</td>
<td>7</td>
<td>-19.27 (11.22)</td>
<td>4.54</td>
<td>6</td>
<td>0.004</td>
</tr>
<tr>
<td>Control</td>
<td>3</td>
<td>-0.1 (6.91)</td>
<td>0.025</td>
<td>2</td>
<td>0.982</td>
</tr>
</tbody>
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Statistics are from SPSS 1-sample t-test of changes in 60, 1-s highest mean arterial pressure (MAP) responses of animals with control lesions and animals with lesions of hypothalamic area controlling emotional responses (HACER).

Fig. 6. Highest 60, 1-s MAP measurements for each session before and after lesion for control (n = 3, dashed lines) and HACER-lesioned animals. Individual number of sessions was truncated at 13 before (sessions 1–13) and 15 after (sessions 15–30) operation, so the number of animals is equal at each point. Break between (sessions 1–13) and HACER-lesioned animals. Individual number of sessions was truncated at 13 before (sessions 15–30) operation, so the number of animals is equal at each point. Break between (sessions 1 and 15) operation, so the number of animals is equal at each point. Break between (sessions 1 and 15) operation, so the number of animals is equal at each point. Break between (sessions 1 and 15) operation, so the number of animals is equal at each point.
imply a qualitative difference in the hypertensive animals that leads to a higher autonomic reactivity to environmental inputs. This species seems to be divided into two groups of animals: those that will develop hypertension and those that will not.

The effect of the HACER lesion on the response to the controlled procedure of cage door opening (Fig. 3) was to reduce the amplitude of the MAP response by 20 mmHg. The control group showed no reduction in the amplitude. Figures 4 and 5 suggest that the perifornical region has an internal functional organization. Although Fig. 4 shows a nearly complete elimination of the total autonomic response, in the animal represented in Fig. 5, only the vasoconstrictor activity is eliminated, leaving the HR response intact. Collectively, these results mirror those obtained earlier in the baboon (21), affirming a cross-species uniformity of the significance of this hypothalamic area in the control of CV responses to emotion-producing situations.

To assess the generality of this result, the 60 highest MAP levels from each of the recorded sessions in which some kind of disturbance had occurred, i.e., feeding, cleaning, cage manipulation, or the cage-door-open procedure, were compared before and after lesion. The results of this analysis show a major reduction in these highest MAP levels in the HACER-lesioned animals in contrast to the control-lesioned animals (Fig. 6). This region of the nervous system is apparently responsible for activating the intense autonomic responses accompanying the psychological experience of emotion, regardless of its source. The major brain region involved in processing emotional experience, especially fear conditioning, is the amygdala (14), and the direct projection from the amygdala to the HACER (4) provides the neural input that excites the perifornical cells. The descending connections of the HACER include the major brain stem and spinal areas important to autonomic control: the periaqueductal gray, ventrolateral reticular formation, nucleus tractus solitarius, parabrachial complex, raphe, and intermediolateral cells of the spinal cord (22), thus providing for maximal autonomic expression.

For a parallel analysis of the lower MAP levels, the 60 lowest MAP measurements were taken from each of the sessions. The effects of the HACER lesion on the lowest pressures in the experimental group were not different, except in animal AG41, which showed a decrease. In general, there is no evidence that the HACER lesion had a demonstrable major effect on the control of blood pressure in nonstressful conditions. This view is supported by the histogram of Fig. 7, which is representative of the four HACER-lesioned animals showing a distinct bimodal distribution pattern that became a unimodal pattern after lesion. The animals with HACER lesions no longer raised their CV levels to the pathological range previously produced by cage door opening or the other “random” events, whereas CV adjustments required for nonstressful activity remained intact.

Of the three animals that were judged to fall into the hypertensive range before the neural procedures, two were in the HACER group and one was in the control group. Although the control-lesioned animal showed a 5-mmHg increase in average maximal MAP across the total data set after lesion, the two HACER-lesioned animals showed 13- and 12-mmHg decreases, representing a substantial amelioration of the overall hypertensive load in these animals.

The question of how these perifornical cells might enter into the production of the hypertensive state provides some interesting considerations. The profound decreases in renal blood flow produced by activating the HACER (20–24) would influence the renal function curve, which is critical to the view of hypertension of Guyton and Coleman (9); the reciprocal anatomic connections between the HACER and the organum vasculosum laminae terminalis and other structures making up...
the lamina terminalis (22) could be important in the fluid balance hypothesis proposed by Osborn (16). The results of the present study may be taken as direct support for Folkow’s classic view (5) on the genesis of essential hypertension as a repetitive “exercise”-type mechanism, and they support Julius and colleagues’ (10–12) emphasis on the role of sympathetic tone as a critical factor in the production of hypertension and metabolic cardiac pathology. Thrasher’s work (26) has revived consideration of the role of the baroreceptors in long-term blood pressure regulation, and the results of McDowall et al. (15) and Zhang et al. (28) point to the possibility that the perifornical area may be exerting a major effect on hypertension through the baroreceptor-resetting mechanism.

In an earlier study utilizing ibotenic acid, instead of electrolytic ablation of the area (23), we provided evidence that the perifornical/lateral hypothalamic cells themselves, and not simply fibers of passage through the hypothalamus, were responsible for the CV responses to stimulation of this area. Further specification of the cells in this region has been made by the identification of the hypocretin/orexin-containing cells (3, 17) that are centrally concentrated in the perifornical/lateral hypothalamic region, which seems to coincide with the anatomic definition of the HACER. Intracerebral injections of orexin produce CV changes (18, 19). Orexin-containing neurons project to various autonomic centers (2, 6), and orexin-knockout mice demonstrate decreased CV and behavioral responses to stress (13); these findings are consistent with the results of the present study, as well as the earlier work (21).

In conclusion, the results of this study show that spontaneously occurring hypertension is found in laboratory housed Aotus monkeys. This hypertension fits a picture of a neurally based essential hypertension and may be engendered by the frequent hyperreactive responses of the sympathetic nervous system of these animals to environmental events. Lesions of the perifornical/lateral hypothalamus (defense area or HACER) block or ameliorate these hyperreactive responses but probably do not interfere with normal nonemotionally influenced CV regulatory adjustments. This perifornical/lateral hypothalamic

Fig. 8. Representative histological sections of the hypothalamic lesions in 3 experimental animals (AG23, AG31, and AG53) and 1 control animal (AG42). Arc, arcuate nucleus; Fx, fornix; Hipp, hippocampus; Inf, infundibulum; LH, lateral hypothalamus; OT, optic tract; PVN, paraventricular nucleus; Sep, septal nuclei; VM, ventromedial nucleus of the hypothalamus.
neural system may play a critical role in the generation and/or progress of some forms of hypertension.

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