Sympathetic Hyperactivity during Hypothalamic Stimulation in Spontaneously Hypertensive Rats

KAZUO TAKEDA and RUBEN D. BUÑAG, *Department of Pharmacology, College of Health Sciences and Hospital, University of Kansas Medical Center, Kansas City, Kansas 66103*

ABSTRACT To determine whether sympathetic hyperactivity of hypothalamic origin contributes to keep blood pressures high in spontaneous hypertension, aortic pressures and sympathetic nerve spike potentials were recorded during electrical stimulation of the posterior hypothalamus in urethane-anesthetized normotensive or hypertensive rats. Basal sympathetic nerve activity was higher in spontaneously hypertensive rats than in either normotensive or deoxycorticosterone acetate-salt hypertensive ones even before stimulation began. Blood pressure elevations produced by hypothalamic stimulation were always preceded by substantial increases in amplitude and rate of neural firing. Changes in amplitude could not be quantified, but rates of neural firing accelerated much more in spontaneous hypertensives than in normotensives during stimulation with 50- and 100-μA currents. Similar differences between deoxycorticosterone acetate-salt hypertensives and either normotensives or spontaneous hypertensives were not statistically significant. Nerve activity invariably became quiescent immediately after hypothalamic stimulation was discontinued, and recovery from this poststimulatory inhibition was faster in spontaneously hypertensive than in normotensive rats. Although spontaneous hypertensives generally also had stronger pressor responses to various sympathomimetic stimuli, responses to hypothalamic stimulation were enhanced to a greater extent than those to either norepinephrine or sympathetic nerve stimulation. Because this selectivity indicates participation of mechanisms other than augmented cardiovascular reactivity, further enhancement of responsiveness to hypothalamic stimuli was attributed to the associated increase in sympathetic nerve firing. These results are in accord with the hypothesis that the blood pressure elevation in rats with established spontaneous hypertension is a result, at least in part, of sympathetic hyperactivity emanating from the posterior hypothalamus.

INTRODUCTION

Spontaneous hypertension in rats has been studied extensively by many investigators because it closely resembles essential hypertension in man. Evidence implicating hypothalamic dysfunction in the blood pressure elevation of the spontaneously hypertensive strain originally bred by Okamoto and Aoki (1) has been published twice previously. First, Yamori and Okamoto (2) found the vasodepressor effects produced by cutting neural connections between the hypothalamus and mesencephalon more pronounced in spontaneously hypertensive than in normotensive rats. Second, Buñag et al. (3) later showed that pressor responses elicited by electrical stimulation of the posterior hypothalamus were larger in awake rats with spontaneous hypertension than in normotensives or in those with deoxycorticosterone acetate-salt (Doca)[1] hypertension. How these differences are caused is uncertain. It is well known that hypothalamic activation augments sympathetic discharge (4–6) and if hypothalamic hyperactivity is partly responsible for spontaneous hypertension then hypothalamic stimulation could increase sympathetic vasomotor discharge more in spontaneously hypertensive than in other rats. To test this assumption we compared spike potentials recorded from sympathetic nerves in spontaneously hypertensive rats during electrical stimulation of the

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Dr. Kazuo Takeda is a postdoctoral research fellow from the Second Department of Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan.

[1] *Abbreviation used in this paper*: Doca, deoxycorticosterone acetate-salt.

posterior hypothalamus with those recorded similarly from normotensive controls. Because we found significant differences in nerve activity, additional experiments were done to determine if sympathetic overactivity was also demonstrable in Doca hypertensive rats.

METHODS

All experiments were done on female Wistar rats purchased from Charles River Breeding Laboratories, Wilmington, Mass. Spontaneously hypertensive and Kyoto-Wistar normotensive rats were from the inbred albino strain originally described by Okamoto and Aoki (1). Doca hypertension was induced in other 1-mo-old outbred rats (3–4 mo before use) by unilateral nephrectomy, subcutaneous implantation of a deoxycorticosterone acetate pellet (25 mg), and substitution of isotonic sodium chloride solution (0.9%) for drinking water; corresponding normotensive controls were of the same strain. Although approximately matched in age (4–5 mo) by the time experiments began, hypertensive rats were smaller than normotensive ones; body weights (g±SEM) averaged 232±7 for outbred normotensives, 230±5 for Kyoto-Wistar normotensives, 212±12 for Doca hypertensives and 198±4 for spontaneous hypertensives (F-ratio of 5.96 with the average for spontaneous hypertensives being significantly lower than any others at a 5% level). Average systolic pressures (mm Hg±SEM) recorded in awake rats with a tail-cuff method (7) before experimentation were 112±4 for outbred normotensives, 128±3 for Kyoto-Wistar normotensives, 162±4 for spontaneous hypertensives, and 215±18 for Doca hypertensives (F-ratio of 23.97 significant at the 1% level). Coaxial electrodes (tip diam 0.5 mm) were implanted using standard stereotaxic techniques at coordinates: anteroposterior 4.6, right lateral 1.0, and dorsoventral −2.5 (8), while the rats were anesthetized with amobarbital sodium (10 mg/100 g i.p.). Electrodes were fixed to the skull with stainless steel screws and dental cement. After electrode implantation, rats were individually caged in an air-conditioned room, fed a standard laboratory chow (Ralston Purina Co., St. Louis, Mo.) ad libitum, and allowed to recover for 1 wk before experiments were attempted.

During experiments, rats were anesthetized with urethane (0.1 g/100 g i.p.). The abdominal plexus was exposed and with the aid of a stereoscopic microscope (Nikon SM-5, Nikon, Inc., Garden City, N. Y.), a bipolar stainless steel electrode (uninsulated tips 1 mm apart) was placed on the major nerve bundle immediately below the coeliac ganglion (9; this is referred to throughout the text as the abdominal sympathetic nerve.). Nerves and electrode tips were immersed in mineral oil to reduce tissue drying. Spike potentials were amplified (Grass P15 AC amplifier, Grass Instrument Co., Quincy, Mass.) and monitored on an oscilloscope (Tektronix 5111, Tektronix, Inc., Beaverton, Oreg.) during recording on magnetic tape (Hewlett-Packard 3960, Hewlett-Packard Co., Palo Alto, Calif.). To reduce noise during nerve recording, spontaneous respiratory movements were abolished by paralyzing skeletal muscles with decamethonium bromide (Syncurine, 0.2 mg/100 g i.v., Burroughs Wellcome Co., Research Triangle Park, N.C.) and a cannula inserted into the trachea was connected to a positive-pressure respirator ventilated with equal mixtures of oxygen and nitrogen (10). Aside from nerve activity, phasic blood pressure was recorded through a cannula inserted in the lower abdominal aorta and connected to a low-volume-displacement pressure transducer (Statham P23Gb, Statham Instruments, Inc., Oxnard, Calif.). Neural and blood pressure data were recorded continuously on magnetic tape before, during, and after hypothalamic stimulation. A square-wave stimulator (Grass S-48, Grass Instrument Co., Quincy, Mass.) with isolation and constant current units was used to deliver 50-, 100-, and 200-μA currents (pulse duration 1 ms, frequency 100/s) in 10-s trains to the hypothalamic electrode. Instead of recording nerve activity, in other experiments changes in blood pressure produced by stimulation of abdominal sympathetic nerves with 10-s trains of 150-μA currents at frequencies of 5, 10, and 20 pulses/s were recorded.

After each experiment, a 2-mA direct current was passed through the hypothalamic electrode for 5 s to produce a small lesion at its tip. Through a thoracotomy, a perfusion needle was inserted into the ascending aorta via the left ventricle; 10% buffered formalin was then perfused into the brain as described by Wolf (11). Excised brains were stored in formalin until sectioning; unstained frozen sections 40-μm thick were cut transversely with a cryotome, and electrode sites examined through a stereomicroscope were compared with the atlas of Pellegrino and Cushman (8). Lesion sites were immediately lateral to the fornix and mamillothalamic tract. In addition to the posterior hypothalamic nucleus, other structures within or adjacent to the terminal lesion included the lateral hypothalamic area, premamillary nuclei, zona incerta, and median forebrain bundle.

Quantification of nerve activity changes is best described by referral to Fig. 1. The top tracing shows original analog signals played back from magnetic tape into the ink-writing recorder; this was fed into an amplitude analyzer (Frederick Haer & Co., Ann Arbor, Mich.) to delete background noise and convert individual spikes into standard pulses in the middle tracing. Because residual activity after ganglion blockade with pentolinium (panel B) or crushing the nerve (panel C) was the same, the low-level control of the window discriminator was routinely set to filter background noise persisting after pentolinium injection. Number of individual pulses per second were counted with a rate analyzer (F. Haer & Co.) whose output was recorded as a histogram (bottom tracing), digitized through a computer interface, and printed by a programmed calculator (Monroe 1860, Litton Industries, Morristown, N. J.). Integrated nerve activity before, during, and after hypothalamic stimulation was obtained by adding the number of spikes per second for 3 s.

Two drugs were injected routinely in all experiments: norepinephrine bitartrate (Levophed, Winthrop Laboratories, Sterling Drug, Inc., New York), 50, 100, and 200 ng (base)/100 g, and pentolinium tartrate (Ansolysen, Wyeth Laboratories, Marietta, Pa.), 0.5 mg (salt)/100 g; both were injected through a jugular vein catheter. The dose of pentolinium used abolished effects of hypothalamic stimulation not only on blood pressure as reported previously (12) but also on sympathetic nerve activity.

Data (expressed as averages ± SE) from all four rat groups were examined with an analysis of variance (13) and for F-ratios significant at 5% or less, Duncan's multiple range test (14) was applied to test for differences between any two of the four groups. To analyze data from only two or three groups (e.g., pressor effects of sympathetic nerve stimulation), t tests for comparing means of independent samples (13) were used, and differences at a 5% level ($P < 0.05$) were considered significant.

RESULTS

Pressor responsiveness to various sympathomimetic stimuli in spontaneously hypertensive and Kyoto-Wistar normotensive rats. Qualitatively similar increases in blood pressure were produced by electrical

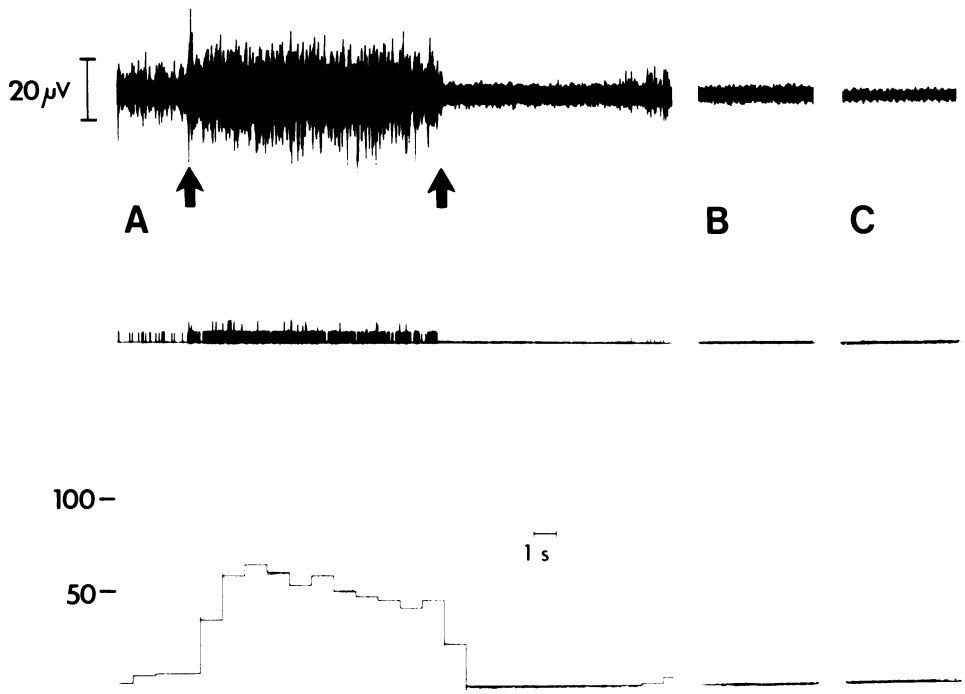

FIGURE 1 Electrical activity from sympathetic nerves of a normotensive rat anesthetized with urethane. The tracings, from top to bottom, are of the original analog signal, the amplitude analyzer (window discriminator) output, and integrated nerve activity. Panel A shows changes produced by hypothalamic stimulation for 10 s (start and finish at arrows); panel B, after ganglion blockade with pentolinium; and panel C, after the nerve had been crushed.

stimulation of either the posterior hypothalamus or abdominal sympathetic nerves, or by intravenous injection of norepinephrine (Fig. 2). The average base line for mean aortic pressure (mm Hg±SEM) of 133±2 for spontaneous hypertensives was significantly higher ($P < 0.001$) than that of 109±1 for normotensives. Magnitude of pressor responses to hypothalamic stimulation was directly related to current strength and was invariably larger in hypertensives than in normotensives. Pressor responses to norepinephrine were dose dependent, but because group differences were not as prominent as those elicited by hypothalamic stimulation, the larger responses of hypertensives differed appreciably from those of normotensives only for doses of 50 and 200 ng/100 g. Similar group differences also occurred with sympathetic nerve stimulation but here again the differences were significant only at stimulation frequencies of 5 and 20 pulses/s. Contrary to our previous findings in unanesthetized rats (3), these results indicate that a general increase in pressor responsiveness is demonstrable in urethane-anesthetized spontaneously hypertensive rats. However, the extent of this increase was not equal in all groups; by coincidence, regardless of which stimulus was applied, normotensives all responded with an average increase of 6 mm Hg to the weakest stimulus strength. In contrast, hypertensives responded to norepinephrine or sympathetic nerve stimulation by only 5 mm Hg more as compared with a 16 mm Hg increase for responses to hypothalamic stimulation. This suggests that peripheral enhancement of cardiovascular reactivity alone cannot account completely for the augmented responsiveness to hypothalamic stimulation.

Sympathetic nerve activity during graded hypothalamic stimulation in hypertensive and normotensive rats. Spike potentials in the abdominal sympathetic nerves were recorded together with aortic pressures before and during graded electrical stimulation of the posterior hypothalamus. Data for normotensive controls were first compiled separately from two groups of rats (five outbred normotensives and six Kyoto-Wistar normotensives), but because group averages thus obtained were almost identical, the results were pooled ($n = 11$). These were then compared with data from eight spontaneously hypertensive and five Doca hypertensive rats. Integrated nerve activity (spikes/3 s) before stimulation was higher in spontaneously hypertensive rats than in normotensive or Doca hypertensive ones; base lines were 42±3 for spontaneous hypertensives as compared with 33±3 for Doca hypertensives ($P < 0.05$) and 26±3 for all normotensives

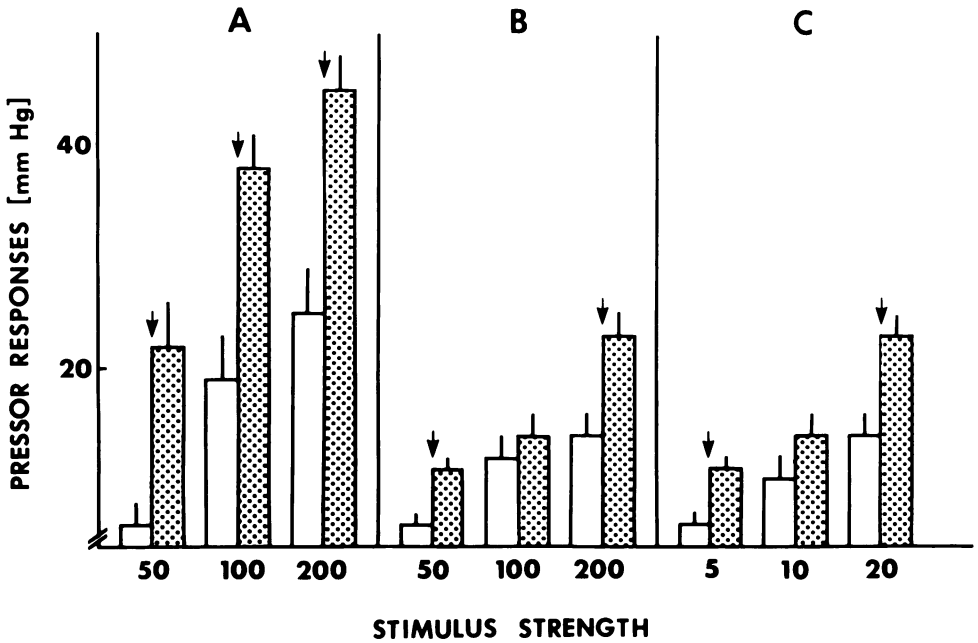

FIGURE 2 Average increases in mean aortic pressure (mm Hg±SEM) above base line produced by various sympathomimetic stimuli in Kyoto-Wistar (open bar) and spontaneously hypertensive (dotted bar) rats. Data averaged from seven rats in each group for hypothalamic stimulation and injected norepinephrine, and from six rats in each group for nerve stimulation. Stimulus strength is indicated by numbers at the bottom in μA for hypothalamic stimulation (A), ng/100 g for injected norepinephrine (B), and pulses per second for sympathetic nerve stimulation (C). Significant differences ($P < 0.05$) between pairs are indicated by arrows.

($P < 0.001$). Rate and amplitude of neural firing both increased precipitously as soon as stimulation started and subsided just as rapidly when stimulation ceased 10 s later (Fig. 1). Nerve activity always increased 0.7–0.9 s before blood pressure rose, and magnitude of both effects was directly proportional to current strength used for stimulation not only in normotensives (Fig. 3) but also in hypertensives (Fig. 4). Although increases in amplitude varied widely from rat to rat and could not be quantified accurately, acceleration of neural firing rate was usually more pronounced in spontaneous hypertensives than in normotensives (e.g., compare increases in Figs. 3 and 4); however, because standard deviations were large differences between groups were statistically significant only during the first 3 s of stimulation with 50 and 100 μA (Table I). In Doca hypertensives such accelerations were intermediate in magnitude but were not significantly different from those in either normotensive or spontaneously hypertensive rats.

By plotting accelerated rates of neural firing against corresponding changes produced in blood pressure during hypothalamic stimulation (Fig. 5), it is evident that for any given increase in sympathetic nerve activity, blood pressure rose more in spontaneously hypertensive than in normotensive rats. The graph

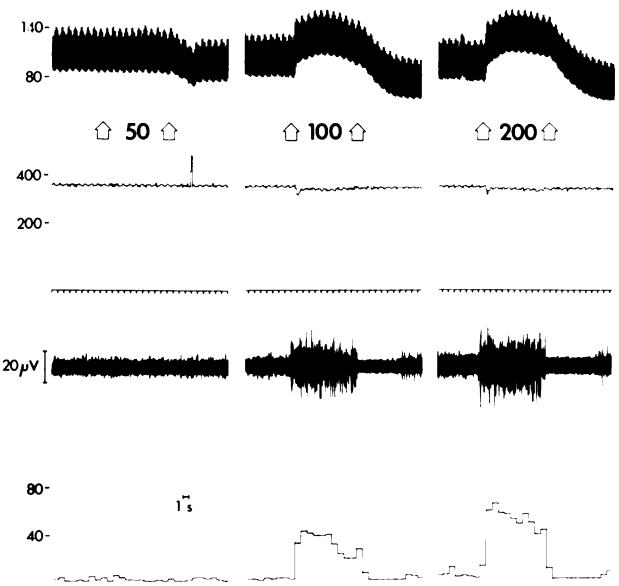

FIGURE 3 Hypothalamic stimulation in an anesthetized Kyoto-Wistar normotensive rat. The tracings from top to bottom are of phasic aortic pressure (mm Hg), heart rate (per minute), original, and integrated (spikes per second) nerve activity. Arrows mark start and finish of hypothalamic stimulation in each panel with the current strength indicated by large numbers.

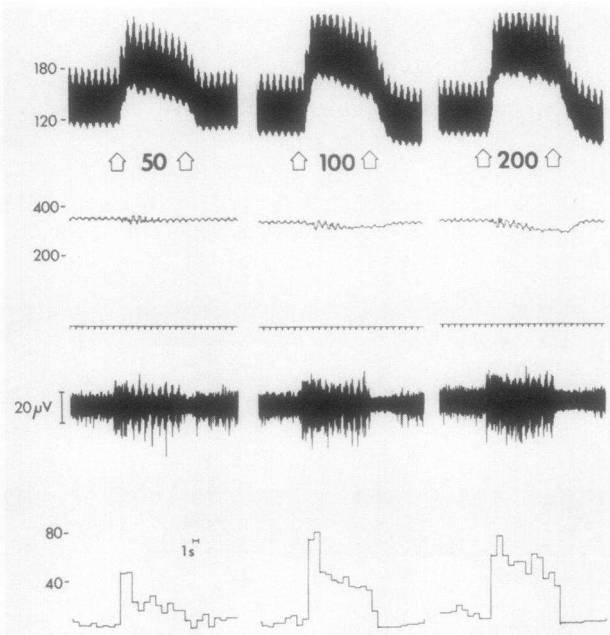

FIGURE 4 Hypothalamic stimulation in an anesthetized spontaneously hypertensive rat. Rest of legend as in Fig. 3.

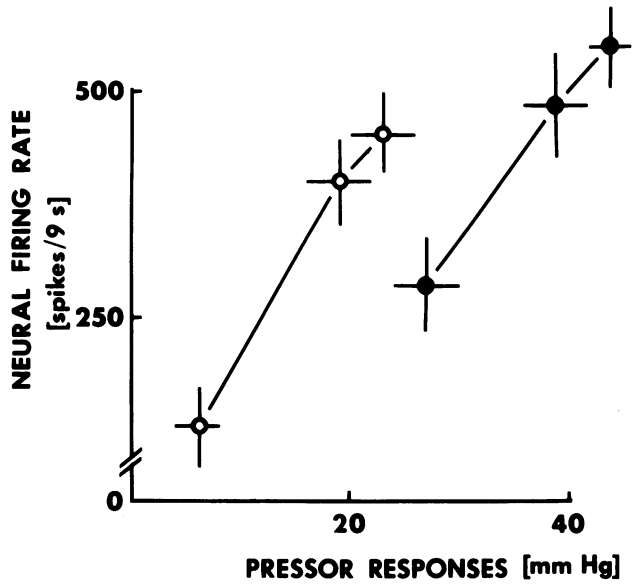

FIGURE 5 Effects of hypothalamic stimulation on sympathetic nerve activity and mean aortic pressure in normotensive (open circles) and spontaneously hypertensive (solid circles) rats. Successive points for each rat group represent average ±SEM increases (nerve activity expressed as the total number of spikes in 9 s) produced by stimulation with 50-, 100-, and 200-μA currents, respectively.

also substantiates the conclusion that group differences in pressor responsiveness to hypothalamic stimulation are not caused solely by increases in cardiovascular reactivity. For instance, an increase of 400 spikes/9 s in neural firing occurred with average pressor responses of 20 mm Hg in normotensives and 30 mm Hg in spontaneous hypertensives; presumably, the 10 mm Hg difference represents enhancement by an increase in cardiovascular reactivity. However, a 20-mm-Hg pressor response in normotensive rats requires stimulating the hypothalamus with 100-μA currents which elicit pressor responses twice as large in spontaneously hypertensive rats (Fig. 2). Accordingly, if increased reactivity accounts for only 10 mm Hg of the augmentation then the remainder must be the result of another mechanism like sympathetic hyperactivity.

TABLE I

Increases in Sympathetic Nerve Firing Rates during Hypothalamic Stimulation in Rats Anesthetized with Urethane

Current strength	Stimulus duration	Rat groups* Normotensive (n = 11)	Spontaneous hypertensive (n = 8)	Doca hypertensive (n = 5)
μA	s			
50	3	37±15	145±29‡	79±26
	6	43±17	84±18	70±27
	9	35±16	57±11	42±13
100	3	153±19	225±27‡	196±26
	6	140±16	142±21	172±30
	9	110±14	120±13	135±36
200	3	173±21	230±26	214±21
	6	153±14	174±17	180±15
	9	127±14	145±9	176±36

* Average±SEM increases over basal levels in spikes/3 s; the number of rats in each group is indicated in parentheses.
‡ $P < 0.05$ as compared with averages for normotensive rats; all other differences were NS.

Nerve activity invariably became quiescent with firing rates falling below basal levels soon after hypothalamic stimulation was discontinued. Although duration of quiescence could not be determined precisely because basal activity returned very gradually, firing rates were always markedly lower than before stimulation began. Magnitude of poststimulatory inhibition was less, and basal activity was recovered earlier, in spontaneous hypertensives than in normotensives (Fig. 6). Both these findings indicate that even after the hypothalamus was no longer being stimulated, sympathetic nerve activity still remained higher in spontaneously hypertensive rats than in normotensive ones.

DISCUSSION

Sympathetic hyperactivity is widely acclaimed as a common pressor mechanism that eventually results in

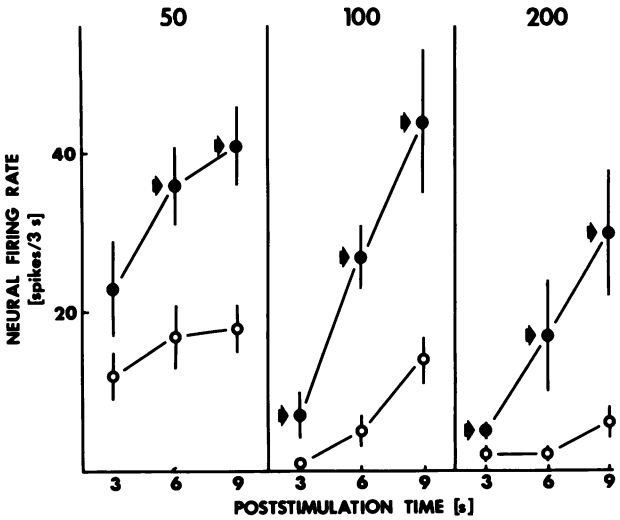

FIGURE 6 Neural firing rates immediately after cessation of hypothalamic stimulation in normotensive (open circles) and spontaneously hypertensive (solid circles) rats. Significant group differences ($P < 0.05$) are indicated by arrows beside the solid circles. Small numbers at the bottom indicate time lapse after stopping stimulation; large ones on top indicate current strengths (μA) used for previous stimulation.

hypertension, but its exact role in spontaneous hypertension has yet to be clearly defined. Its initial involvement as a 'trigger' mechanism is suggested by the consistent finding that immuno- or chemical sympathectomy in young spontaneously hypertensive rats inhibits the subsequent elevation of blood pressure (15–18). Contradicting the idea that sympathetic hyperactivity merely initiates development of hypertension (19, 20), however, our present results show that sympathetic tone is greater than normal in adult spontaneously hypertensive rats. Others have similarly found larger sympathetic action potentials in these rats (21, 22) and it has also been reported that their splanchnic nerves had to be stimulated at higher frequencies than those in normotensive rats to restore blood pressures after sympathectomy (23). Additionally, stronger vasoconstrictor responses to splanchnic nerve stimulation have been shown in mesenteric arteries from spontaneously hypertensive rats than in those from renal hypertensive ones (24). On the other hand, Lais, et al. (25) found no differences in either neural activity or vasoconstrictor response of perfused hindquarter preparations to stimulation of lumbar sympathetic chains. Although varying methods for anesthesia and nerve recording may be partly to blame, much of the discrepancy seems to be a result of differences in nerves studied. Unlike the lumbar sympathetic chains (which supply somatic structures) studied by Lais et al., the sympathetic nerves studied by everyone else innervate visceral structures. Because electrical activity varies from one sympathetic nerve to another depending upon the structure supplied (26; e.g., baroreceptors regulate neural traffic to kidneys but not that to skin), electrical discharges in visceral sympathetic nerves probably differ considerably from those in lumbar sympathetic chains. Regardless of the discrepancy, the bulk of current evidence, including that presented here, indicates that sympathetic vasomotor tone remains elevated even after spontaneous hypertension has been established for some time.

The present findings cannot be artifacts caused by anesthesia because enhanced hypothalamic pressor responsiveness has been observed repeatedly even in awake or unanesthetized spontaneously hypertensive rats (3, 27). In normotensive rats, pressor responses to hypothalamic stimulation are slightly increased by urethane anesthesia but unaffected by positive-pressure respiration or drug-induced neuromuscular blockade (28); an appreciable effect of these experimental conditions on the results described here is, therefore, unlikely.

Notwithstanding species differences our results agree remarkably well with those from anesthetized cats (4, 5). Long ago Pitts et al. (6) had shown also in cats that blood pressure and sympathetic nerve activity both increased during hypothalamic stimulation, and that magnitude of pressor responses was graded by increasing not only the numbers but also the firing rates of actively firing neurons. In line with this, the differences we produced by stimulation with 50- and 100-μA currents could mean that active neurons were more numerous and also firing faster in spontaneous hypertensives than in normotensives. Conversely, if saturation caused by stimulation with 200-μA currents caused all the neurons in our multifiber preparation to fire maximally, than any slight differences that may exist between hypertensive and normotensive rats would not be readily evident. Nonetheless, despite dwindling differences in sympathetic nerve discharge, pressor responses to stimulation with 100- and 200-μA currents were still more pronounced in spontaneous hypertensives than in normotensives (see Figs. 2 and 5). Perhaps when firing rates are already high further increases in nerve firing elevate blood pressure more in spontaneously hypertensive rats because the structural increase in wall:lumen ratio of the resistance vessels (29) causes stronger vasoconstriction even in response to equal stimuli.

Thus, the most cogent finding presented here is that appropriate hypothalamic stimulation increases sympathetic vasomotor activity more in spontaneously hypertensive rats than in others. This interpretation is supported not only by the finding of faster neural firing rates during hypothalamic stimulation, but also by the weaker inhibition ensuing immediately after stimulation was discontinued. It can still be argued that

stimulation of a hypersensitive hypothalamus may increase blood pressure only temporarily and unless some other hypertensive mechanism intervened, blood pressure would return to normal whenever stimulation stopped. Various stresses (noise, restraint, light, or vibration) increase blood pressure more in spontaneously hypertensive than in normotensive rats (20, 30) but whether the elevation eventually persists is unknown. With repeated hypothalamic stimulation pressor responses remain enhanced in awake spontaneously hypertensive rats, but basal pressure levels are unchanged even after several hours (27). More prolonged hypothalamic stimulation like that which has been used to elevate systolic pressure progressively in normotensive rats (31) could conceivably exacerbate development or maintenance of spontaneous hypertension.

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