Exaggerated Sympathetic Responses to Bradykinin in Spontaneously Hypertensive Rats

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SUMMARY Possible defects in blood pressure (BP) regulation were studied by recording responses to centrally-administered bradykinin. Pressor effects accompanied by increased sympathetic nerve activity were elicited by intracerebroventricular injections in intact rats, but significant differences between Kyoto-Wistar normotensive (KNR) and spontaneously hypertensive rats (SHR) were not detected. By contrast, intracarotid injections into cross-perfused head preparations consistently produced more prominent systemic effects in SHR than in KNR, and these differences became even more pronounced following carotid denervation. After destruction of central noradrenergic neurons in KNR by intracerebroventricular injection of 6-hydroxydopamine (6-OHDA), responses to bradykinin became the same as those in SHR. These results are in accord with the interpretation that α-adrenergic mechanisms for blood pressure regulation in supramedullary brain areas no longer function normally in SHR and that a similar dysfunction can be induced in KNR by pretreatment with 6-OHDA. (Hypertension 3: 433-440, 1981)

KEY WORDS • Blood pressure • 6-hydroxydopamine • spontaneous hypertension • supramedullary brain centers • sympathetic nerve activity

ALTHOUGH sympathetic hyperactivity has been consistently demonstrated in SHR, the site from which it arises is unknown. A central origin is suggested by studies showing that blood pressure (BP) changes caused by destruction or stimulation of certain brain areas are more pronounced in SHR, but these findings could just as easily be explained by peripheral increases in cardiovascular reactivity. To eliminate the possibility of peripheral mediation, we previously used a cross-perfused head preparation in which systemic effects of test drugs injected into the head of a recipient rat could be transmitted to its body only via the spinal cord. Because phenylephrine lowered the BP and sympathetic nerve activity more prominently in SHR, in accord with the hypothesis proposed by Yamori et al., we concluded that α-adrenergic vasodepressor mechanisms in supramedullary brain areas no longer function normally in SHR.

More recently we found that, in cross-perfused head preparations from normotensive rats, bradykinin has at least two centrally-mediated effects on BP: 1) an initial vasodepression caused by release of endogenous norepinephrine, which activates α-adrenergic vasodepressor mechanisms in supramedullary centers; and 2) a secondary pressor response, probably caused by release of endogenous prostaglandins. Pursuing this further, we designed the present studies to characterize responses to centrally-administered bradykinin in KNR and SHR. Based on the assumption that enhanced responsiveness to bradykinin in SHR results from dysfunction of α-adrenergic mechanisms in the brain, we conducted additional experiments to determine whether a similar enhancement in responsiveness could be induced in KNR by destroying central noradrenergic neurons through the intracerebroventricular injection of 6-OHDA.

Methods

Two groups of Kyoto-Wistar rats, descended from the inbred Okamoto and Aoki strains were purchased from Taconic Farms, Inc. (Germantown, New York): 16-week old females for intracerebroventricular injections and 12-week old males for cross perfusion. Body weights for females averaged 213 ± 7 g for KNR (n = 8) and 211 ± 7 g for SHR (n = 8); corresponding averages among males were 235 ± 3 g (n = 59) and 222 ± 3 g (n = 73) respectively. Systolic
pressures determined routinely in all rats with a tailcuff method \(^1\) 1 week before experimentation averaged 136 ± 3 mm Hg in KNR and 185 ± 4 mm Hg in SHR.

**Intraerebroventricular Injections in Intact Rats**

Rats were anesthetized with methoxyflurane while a guide cannula (23 gauge stainless steel tubing, 1.5 cm long) was inserted into the left lateral ventricle (at stereotaxic coordinates 5.6 anteroposterior, 1.6 lateral, and +2.0 dorsoventral, with the upper incisor bar set 5 mm above the interaural line \(^2\)) and fixed to the skull using screws and dental cement. After allowing 1 week to lapse, each rat was reanesthetized with methoxyflurane while an indwelling catheter was inserted into the caudal artery. One hour later, with the rat awake but placed in a restrainer, the blood pressure (BP) was recorded continuously by connecting the caudal catheter to a pressure transducer (Statham P23Gb). Bradykinin was injected by inserting an injection cannula (30-gauge tubing) connected to a 10 μl syringe mounted on an infusion pump into the guide cannula. The whole system was filled with the solution to be injected, and each injection had a volume of 10 μl delivered at a pump rate of 10 μl/min. Subsequently, each rat was anesthetized with urethane (50 mg/100 g IV), prepared for splanchnic nerve recording as described below, and intraventricular injection of bradykinin was repeated. At the end of most experiments, methylene blue was injected through the injection cannula to verify the correct placement of the cannula tip within the left lateral ventricle.

**Cross-Perfused Head Preparation**

For each preparation, three rats were anesthetized with urethane (100 mg/100 g IP or 50 mg/100 g IV): one supplied blood for priming extravascular connections, while the others served as the donor and recipient respectively. Phasic arterial pressure was recorded continuously from femoral catheters in both rats. The recipient's head was vascularly isolated from its body by connecting both jugular veins and common carotid arteries through a peristaltic pump, to corresponding vessels of the donor. As soon as one carotid cannula was inserted in the recipient, it was temporarily connected to the femoral artery to allow continued supply of arterial blood to the head while the remaining carotid was being cannulated; hypoxia resulting from interruption of cerebral blood flow was thus kept at a minimum. Pump speed was adjusted to keep carotid pressure at the same level as that of the femoral pressure, and perfusion pressure was recorded routinely downstream from the pump through a side-arm of the carotid circuit. Leakage from head to body, as estimated from radioactivity in the body following intracarotid injection of bovine serum albumin labeled with iodine-125, averaged 18.7 ± 1% in KNR and 15.4% ± 2% in SHR. Total dead space (venous and arterial connections including catheters) of 2 ml was filled with heparinized blood (500 U/100 g).

Respiratory rate and amplitude in the recipient were recorded by connecting the side-arm of a tracheal cannula to a pressure transducer.

**Recording of Sympathetic Nerve Activity**

The abdominal plexus was exposed through a ventral transverse incision, and the inferior nerve bundle, emerging from the coeliac ganglion and accompanying the superior mesenteric artery, was placed over a bipolar stainless steel electrode ( uninsulated tips 1 mm apart). Nerves and electrode tips were immersed in mineral oil to prevent tissue drying. To reduce noise during nerve recording, spontaneous respiratory movements were abolished by paralyzing skeletal muscles with decamethonium bromide (Syncurine, 0.2 mg/100 g IV) and by connecting the recipient to a respirator ventilated with a mixture of 50% oxygen and 50% nitrogen. Spike potentials were amplified (Grass P15AC amplifier), monitored on a storage oscilloscope, and recorded continuously on magnetic tape. Tapes were later played back into an amplitude analyzer (Haer and Company, Brunswick, Maine) to delete background noise and convert individual spikes into uniform pulses. The number of individual pulses per second was counted with a rate analyzer whose output was recorded as a histogram on an ink-writing recorder, converted to digital form using a computer interface, and printed by a programmed calculator. Integrated nerve activity during and after injections of bradykinin is expressed as the total number of spikes in 15 or 30 seconds.

**Drug Injections, Carotid Denervation, and Vagotomy**

For intraventricular injections, bradykinin was dissolved in artificial cerebrospinal fluid (CSF) using Elliott’s B solution in which each ml contained 7.3 mg sodium chloride, 1.9 mg sodium bicarbonate, 0.8 mg dextrose, 0.3 mg magnesium sulfate, 0.3 mg potassium chloride, 0.2 mg calcium chloride, 0.2 mg sodium phosphate, and 0.1 μg phenol sulphonaphthalein. For cross perfusion experiments, bradykinin dissolved in 0.9% sodium chloride solution was injected into the carotid circuit in a volume of 10 μl; doses are expressed as 0.01 to 10 μg of salt (bradykinin triacetate) injected per rat. Whenever sympathetic nerve activity was recorded, pentolinium tartrate (Anosylen), 0.5 mg (salt)/100 g IV, was injected at the end of the experiment to determine the residual activity and setting of the low-level control of the window discriminator during playback.

For pretreatment with 6-OHDA, KNR rats that had been debuffered 1 week earlier were anesthetized with methoxyflurane, and a guide cannula was inserted into a lateral ventricle. A 30-gauge injection cannula connected to a microliter syringe was then inserted through the guide cannula in five rats for intraventricular injection of 6-hydroxydopamine hydrobromide (Sigma Chemical Company; 250 μg in 1% ascorbic acid solution per rat). Each injection con-
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Intracerebroventricular Injections in Intact Rats

Intracerebroventricular injections of bradykinin, 1 \( \mu g \), became maximal within 2 minutes and lasted for about 10 minutes. The magnitude of both effects seemed slightly larger in SHR than in KNR, but none of the differences was significant (table 1).

Upon subsequent induction of urethane anesthesia, the difference in MAP baselines was maintained (124 ± 6 in KNR and 183 ± 9 mm Hg in SHR; \( p < 0.001 \)), but heart rate became inexplicably higher in KNR (381 ± 13 beats/min) than in SHR (329 ± 9 beats/min; \( p < 0.005 \)). Corresponding baselines for the frequency of sympathetic nerve firing were slightly lower in KNR (608 ± 56 spikes/30 sec) than in SHR (752 ± 65 spikes/30 sec; \( p > 0.1 \)). To elicit appreciable pressor effects by ICV injection, doses of bradykinin had to be increased tenfold. However, although the effects on MAP, heart rate, and sympathetic nerve firing all seemed larger in SHR than in KNR (table 1), differences were not statistically significant.

Effects of Bradykinin in Cross-Perfused Head Preparations

Despite initially large differences between KNR and SHR in tail-cuff systolic BP, smaller differences in femoral MAP were recorded after urethane anesthesia and completion of the surgical preparation for cross perfusion. At an F ratio for BP of 18.69 (significant at 1%), the differences between KNR and SHR, whether intact or denervated, were consistently higher than the corresponding R values at 1%. This means that SHR always had significantly higher BPs than KNR, and that in both groups the differences were unaffected by carotid denervation (table 2). On the other hand, the F ratio for the heart rate of 6.82 was also significant at 1%, with the difference between intact and denervated KNR being higher than the corresponding R value at 1%; however, a similar difference between intact and denervated SHR was not significant. Differences in baselines for sympathetic nerve activity were generally inconsequential except for that between intact SHR and intact KNR, which were significant at 5%.

<table>
<thead>
<tr>
<th>Rat Groups</th>
<th>KNR</th>
<th>SHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable measured</td>
<td>(n = 7)</td>
<td>(n = 7)</td>
</tr>
<tr>
<td>Awake:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>blood pressure (mm Hg)</td>
<td>21 ± 4</td>
<td>34 ± 6</td>
</tr>
<tr>
<td>heart rate (beats/min)</td>
<td>38 ± 4</td>
<td>41 ± 5</td>
</tr>
<tr>
<td>Anesthetized:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>blood pressure (mm Hg)</td>
<td>8 ± 2</td>
<td>16 ± 3</td>
</tr>
<tr>
<td>heart rate (beats/min)</td>
<td>10 ± 3</td>
<td>29 ± 7</td>
</tr>
<tr>
<td>nerve activity (spikes/30 sec)</td>
<td>44 ± 18</td>
<td>141 ± 82</td>
</tr>
</tbody>
</table>

*Data expressed as average ± SEM changes from the baselines given in the text following intracerebroventricular injections of bradykinin, 1 \( \mu g \) for awake and 10 \( \mu g \) for anesthetized rats.
TABLE 2. Baselines for Intact or Denervated KNR and SHR Used as Recipients in Cross-Perfusion Experiments

<table>
<thead>
<tr>
<th>Measurement</th>
<th>KNR intact</th>
<th>KNR denervated</th>
<th>SHR intact</th>
<th>SHR denervated</th>
<th>P-ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>blood pressure (mm Hg)</td>
<td>78 ± 6</td>
<td>70 ± 4</td>
<td>102 ± 9</td>
<td>102 ± 2</td>
<td>18.69</td>
</tr>
<tr>
<td>heart rate (beats/min)</td>
<td>423 ± 11</td>
<td>330 ± 16</td>
<td>384 ± 12</td>
<td>337 ± 11</td>
<td>6.82</td>
</tr>
<tr>
<td>respiration (/min)</td>
<td>83 ± 4</td>
<td>56 ± 4</td>
<td>98 ± 15</td>
<td>64 ± 7</td>
<td>2.83</td>
</tr>
<tr>
<td>nerve firing (spikes/15 sec)</td>
<td>217 ± 11</td>
<td>221 ± 14</td>
<td>265 ± 17</td>
<td>255 ± 9</td>
<td>3.24</td>
</tr>
</tbody>
</table>

Data from five intact KNR, nine denervated KNR, five intact SHR, and 17 denervated SHR. With f1 = 3 and f2 = 32, F ratios of 4.46 or more are significant at 1%, and of 2.90 or more at 5%.

Responses to intracarotid injections of bradykinin of recipient rats, regardless of their grouping, were complex and varied depending on the doses injected into the isolated head. Carotid perfusion pressure was invariably reduced (by about 30 to 40 mm Hg) within 1 to 2 seconds after injection; for effective doses, subsequent changes in femoral BP appeared a few seconds later. With carotid innervation intact, doses of 1 and 10 μg had biphasic effects on femoral BP consisting of an initial fall followed by a secondary and more sustained rise after a few seconds. Lower doses were either ineffective (0.01 μg) or purely hypotensive (0.1 μg). Dose-dependent reductions in heart rate occurred regularly during the initial hypotensive phase, but changes during the secondary pressor phase were small and inconsistent. In both KNR and SHR, bilateral vagotomy prevented the bradycardia without affecting the BP response. Respiratory depth and rate were also increased more markedly in SHR than in KNR (table 3). The frequency of sympathetic nerve firing was almost always slightly reduced during the initial hypotensive phase; however, this reduction lasted for only 1 or 2 seconds and could not be quantified. During the secondary pressor phase, neural firing was invariably accelerated, with the magnitude of the increase being dose-dependent. Donor rats were unaffected except by the 10 μg dose, which lowered femoral BP by about 10 mm Hg.

Following carotid denervation, responses to bradykinin became purely pressor, and their magnitude was much more prominent in SHR (table 3). All F ratios comparing responses recorded from the four subgroups studied were significant at 1%, thereby indicating that one or more of the subgroups differed from the rest. For changes in BP, the initial vasodepression occurred consistently in intact rats but was abolished.

TABLE 3. Cardiovascular, Respiratory, and Sympathetic Nerve Responses to Bradykinin in Intact and Denervated KNR and SHR

<table>
<thead>
<tr>
<th>Rat groups</th>
<th>Dose (μg)</th>
<th>Blood pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>respiration (/min)</th>
<th>Nerve firing (spikes/15 sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KNR</td>
<td></td>
<td>initial</td>
<td>sustained</td>
<td>0</td>
<td>-2 ± 7</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td>-11 ± 3</td>
<td>-11 ± 3</td>
<td>0</td>
<td>-2 ± 7</td>
</tr>
<tr>
<td>intact</td>
<td>1.0</td>
<td>-10 ± 3</td>
<td>-7 ± 3</td>
<td>0</td>
<td>4 ± 11</td>
</tr>
<tr>
<td></td>
<td>10.0</td>
<td>-9 ± 4</td>
<td>-1 ± 4</td>
<td>2 ± 1</td>
<td>7 ± 13</td>
</tr>
<tr>
<td>KNR</td>
<td>0.1</td>
<td>0</td>
<td>6 ± 1</td>
<td>8 ± 2</td>
<td>9 ± 3</td>
</tr>
<tr>
<td>denervated</td>
<td>1.0</td>
<td>16 ± 3</td>
<td>25 ± 3</td>
<td>20 ± 6</td>
<td>126 ± 61</td>
</tr>
<tr>
<td></td>
<td>10.0</td>
<td>22 ± 4</td>
<td>47 ± 4</td>
<td>21 ± 5</td>
<td>347 ± 42</td>
</tr>
<tr>
<td>SHR</td>
<td>0.1</td>
<td>-8 ± 3</td>
<td>-6 ± 2</td>
<td>0</td>
<td>29 ± 10</td>
</tr>
<tr>
<td>intact</td>
<td>1.0</td>
<td>-7 ± 2</td>
<td>5 ± 3</td>
<td>6 ± 1</td>
<td>63 ± 16</td>
</tr>
<tr>
<td></td>
<td>10.0</td>
<td>-5 ± 2</td>
<td>15 ± 3</td>
<td>12 ± 3</td>
<td>53 ± 10</td>
</tr>
<tr>
<td>SHR</td>
<td>0.1</td>
<td>33 ± 5</td>
<td>33 ± 4</td>
<td>69 ± 11</td>
<td>148 ± 46</td>
</tr>
<tr>
<td>denervated</td>
<td>1.0</td>
<td>61 ± 5</td>
<td>45 ± 4</td>
<td>117 ± 14</td>
<td>421 ± 99</td>
</tr>
<tr>
<td></td>
<td>10.0</td>
<td>63 ± 5</td>
<td>50 ± 6</td>
<td>120 ± 7</td>
<td>846 ± 204</td>
</tr>
</tbody>
</table>

All values expressed as average ± SEM changes from baselines given in table 2. F ratios comparing averages from the four subgroups are all greater than 5.29 and therefore significant at 1%.
in denervated ones, whether in KNR (fig. 1) or SHR (fig. 2). The secondary pressor phase was all that remained after denervation and was much more pronounced in SHR than in KNR; at all dose levels of bradykinin, differences between the sustained pressor effect in denervated SHR and that in other rats were consistently larger than the corresponding R values at 1%. Cardioacceleration occurred during the secondary pressor phase in all denervated rats (table 3), with its magnitude being larger in SHR than in KNR. Heart rate changes during the initial hypotensive phase were slight and did not differ between groups. Hyperpnea induced by bradykinin was also enhanced by carotid denervation, particularly in SHR (table 3). With the single exception of the 0.1 μg dose in intact KNR, the frequency of the sympathetic nerve firing increased appreciably, and despite wide variations from rat to rat, the magnitude of this increase was higher in denervated SHR than in any of the other three subgroups (differences obtained with the multiple range test were invariably larger than the corresponding R values at 5%).
Discussion

Two of our findings suggest that brain mechanisms for cardiovascular regulation are deranged in SHR. First, pressor and sympathetic nerve responses elicited by injecting bradykinin into the cross-perfused head were more pronounced in SHR than in KNR. Second, KNR, whose central noradrenergic neurons had been destroyed through intracerebroventricular injections of 6-OHDA, showed subsequent responses to bradykinin that quantitatively resembled those in SHR. Both these findings support our previous contention that α-adrenergic mechanisms for regulating BP in supramedullary brain areas no longer function normally in SHR.

Most systemic effects produced by injecting bradykinin into the cross-perfused head must result from actions on the brain. Carotid blood flow in such preparations goes primarily to the hypothalamus, cerebrum, and midbrain, and, if bradykinin is distributed similarly, then it could reach circumventricular areas like the median eminence, organum vasculosum of the lamina terminalis, subfornical organ, or choroid plexus, which are devoid of a blood-brain barrier and would therefore allow crossing of solutes regardless of molecular size or lipid solubility. In normotensive rats, ensuing effects on BP are biphasic, consisting of an initial transient fall followed by a more prolonged secondary elevation. The initial fall together with its attendant decrease in sympathetic nerve activity are abolished following intracerebroventricular injection of 6-OHDA, and are consequently attributed to activation of α-adrenergic vasodepressor mechanisms by endogenous norepinephrine released in the brain by bradykinin. On the other hand, the more sustained pressor response is invariably accompanied by increased sympathetic nerve activity; because both effects are reduced following inhibition of prostaglandin synthesis with indomethacin, and augmented
following pretreatment with the prostaglandin precursor, arachidonic acid, they are ascribed to endogenous prostaglandins released in the brain by bradykinin. Presumably, the endogenous chemical mediators thereby released would in turn act on responsive brain centers that influence sympathetic vasomotor tone and BP via descending intermediolateral pathways in the spinal cord.

Carotid denervation obviously has variable effects on the response to centrally-administered bradykinin, because the initial vasodepression was augmented in ordinary Wistar rats but, on the contrary, was abolished in the Kyoto-Wistar rats studied here. While this implies that carotid buffer nerves do not function in exactly the same way in different rat strains, underlying mechanisms are unknown. Stimulation by bradykinin of either pressoreceptors or chemoreceptors could be involved, since subsequent effects of denervation would result from destruction of afferent nerve fibers coming from either the carotid sinuses or bodies. It is quite likely that carotid pressoreceptors have already been disabled because neither systemic BP nor nerve activity are appreciably altered when carotid perfusion pressure is mechanically elevated in cross-perfused head preparations. Thus, a possible explanation for the initial vasodepression caused by bradykinin is that, like responses described previously in cats or dogs, it is due to chemoreceptor stimulation and therefore abolished by carotid denervation. However, this would not account for all the differences between intact KNR and SHR since SHR had larger respiratory but smaller vasodepressor responses to bradykinin, thereby implying that, while chemoreceptor sensitivity was increased to heighten respiratory responses, it was simultaneously decreased to reduce vasodepressor ones.

It may be easier to explain differences in vasodepressor responsiveness to bradykinin based on changes in brain catecholamine content. Because perfused head preparations from SHR also have enhanced vasodepressor responses to phenylephrine, one might expect a similar enhancement of the initial vasodepression caused by bradykinin. But unlike phenylephrine, which acts directly on \( \alpha \)-adrenergic receptors, the evidence now available indicates that bradykinin acts indirectly by releasing endogenous norepinephrine, and it can be argued that since SHR are more responsive to central \( \alpha \)-adrenergic stimulation with phenylephrine, they should also be more responsive when the same receptors are stimulated indirectly by bradykinin. Contradicting this, we found magnitude of vasodepressor responses to bradykinin slightly lower in SHR than in KNR (with intact carotid innervation; see table 3). Actually, the discrepancy may be more apparent than real because, with diminished hypothalamic levels of norepinephrine, SHR may have less norepinephrine available for release by bradykinin. That depressor mechanisms in the anterior hypothalamus are deficient in SHR was recently suggested by Wijnen et al., who found norepinephrine concentrations in the anterior hypothalamus markedly reduced in SHR.

Many mechanisms probably contribute to enhance "pressor responsiveness in SHR, but the extent to which each mechanism participates is difficult to judge. Usually included among mechanisms considered important are peripheral increases in either reactivity (as a consequence of adaptive wall hypertrophy, particularly in resistance vessels) or adrenergic mediators released from sympathetic nerve endings. Although both mechanisms could conceivably be involved in enhancing pressor responsiveness to bradykinin (table 3), neither one can account for the accompanying acceleration in sympathetic nerve firing, which was consistently more pronounced in SHR than in KNR. As has already been mentioned, endogenous prostaglandins released in the brain by bradykinin could account for these effects by acting on responsive brain areas to increase sympathetic nerve activity and thereby cause further enhancement of pressor responsiveness. This prostaglandin-mediated pressor phase cannot be totally dissociated from the preceding \( \alpha \)-adrenergic vasodepression but may instead be masked by it. When \( \alpha \)-adrenergic mechanisms operate normally, as in normotensive rats, the initial vasodepressor response to bradykinin may be strong enough to partly restrain the subsequent pressor phase. But when such mechanisms no longer function efficiently, as in SHR, then as the initial vasodepressor response is reduced and normal restraint is lost, the prostaglandin-mediated pressor phase becomes accentuated. According to this interpretation, therefore, pressor responsiveness in SHR could be enhanced because the inhibition normally exerted by \( \alpha \)-adrenergic vasodepressor mechanisms in the brain no longer exists. Alternatively, it is also possible that endogenous brain prostaglandins somehow work differently in SHR.

Perhaps our most provocative finding is the demonstration that KNR can be made to respond to bradykinin like SHR by pretreatment with 6-OHDA (table 4). To restrict norepinephrine depletion to the brain, 6-OHDA was given by intracerebroventricular injection and in doses that had been shown effective in reducing brain norepinephrine levels markedly. If a cause-and-effect relationship indeed exists between the reduction in brain norepinephrine produced by 6-OHDA and the quantitative conversion of pressor responses to bradykinin from those characterizing KNR to those of SHR, then the implication is that a similar state of dysfunction has been induced. In other words, conversion of responses to bradykinin following destruction of central noradrenergic neurons with 6-OHDA implies that a failure in BP regulation by the brain similar to that existing in SHR has artificially been induced in KNR. Despite this effect, however, 6-OHDA cannot be used alone to induce spontaneous hypertension, not only because it has other effects (e.g., loss of body weight and depletion of amines other than norepinephrine) which could modify or prevent the changes in BP, but also because bulboispinal noradrenergic mechanisms responsible for maintaining sympathetic vasomotor tone may also be destroyed.
References

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